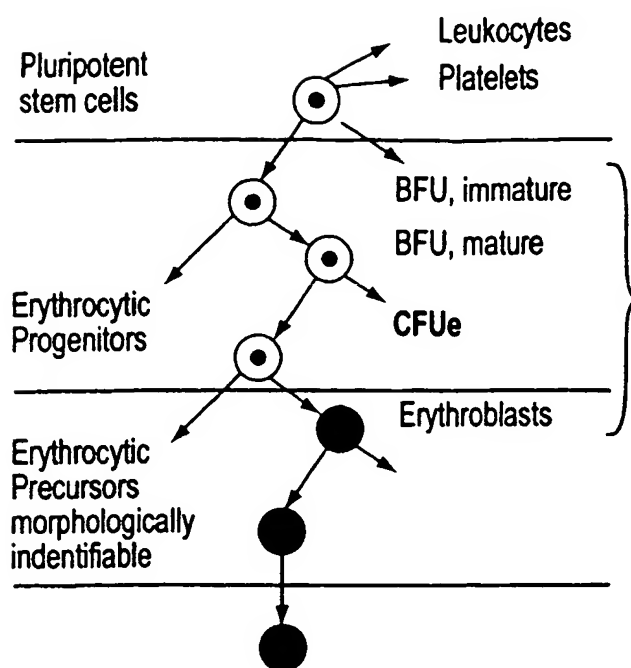


## Erythropoiesis



EPO is believed to

- Stimulate the proliferation and differentiation of committed erythroid cells
- Prevent the apoptosis of erythrocytic progenitors
- Increase the viability of erythrocytes

FIG. 1

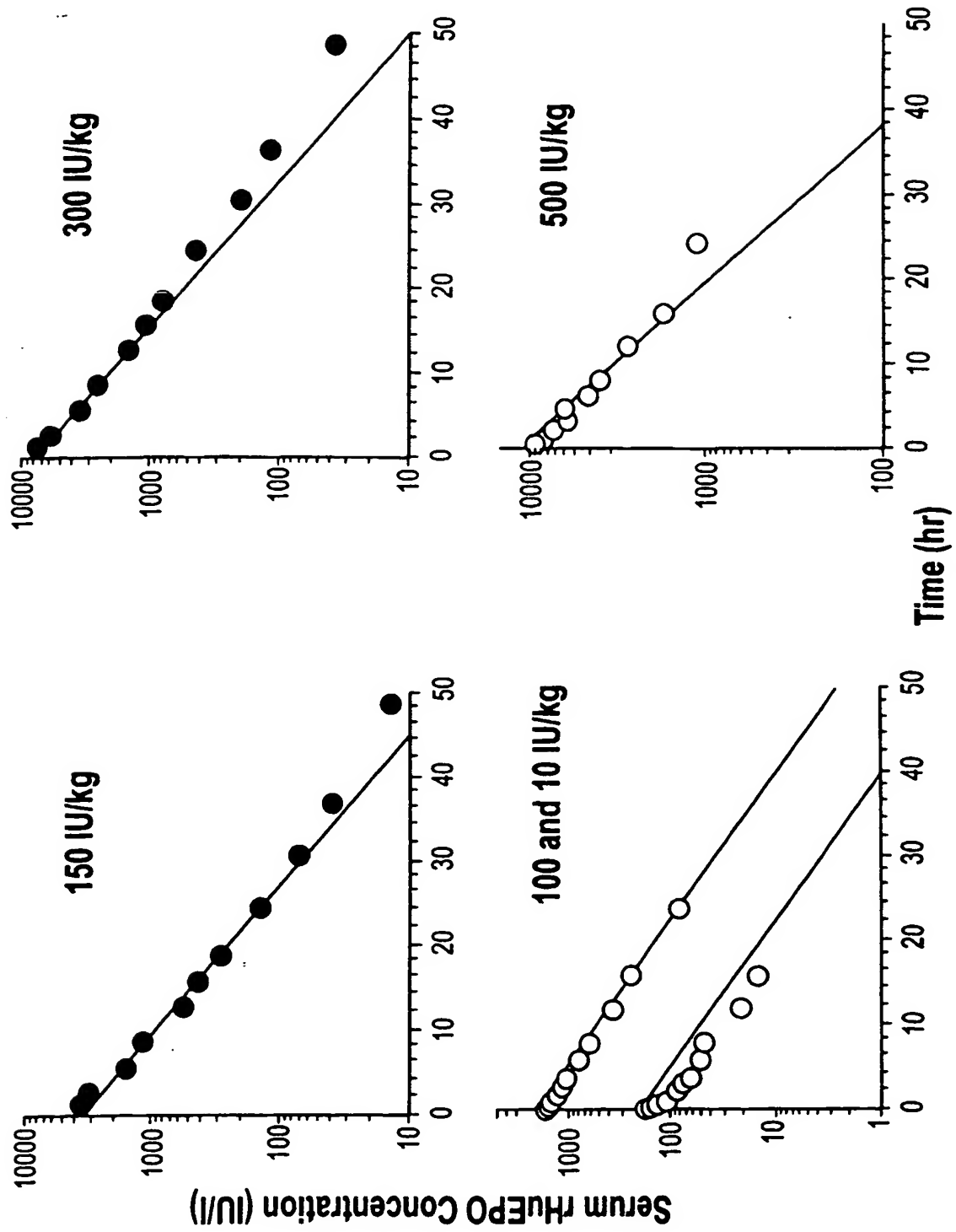


FIG. 2

## PHARMACOKINETIC PARAMETERS FOR INTRAVENOUS AND SUBCUTANEOUS EPO DOSES

PARAMETER	ESTIMATE	CV%
Vmax (IU/hr)	138.5	
Km (IU/l)	20940	
Vd (l/kg)	0.0558	
ka (hr <sup>-1</sup> )	0.0219	4.836
Fr	0.131	7.291
$\tau$ (Lower doses, hr)	44	
$\tau$ (Higher doses, hr)	60	

FIG. 3

## PHARMACOKINETIC MODEL

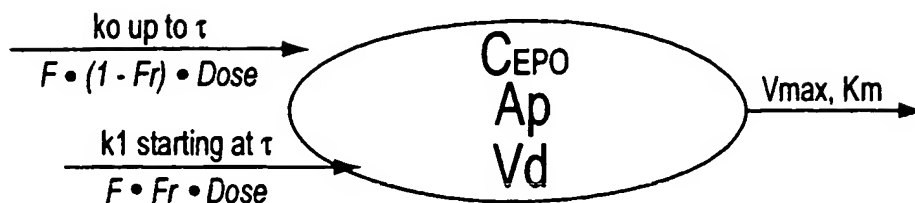
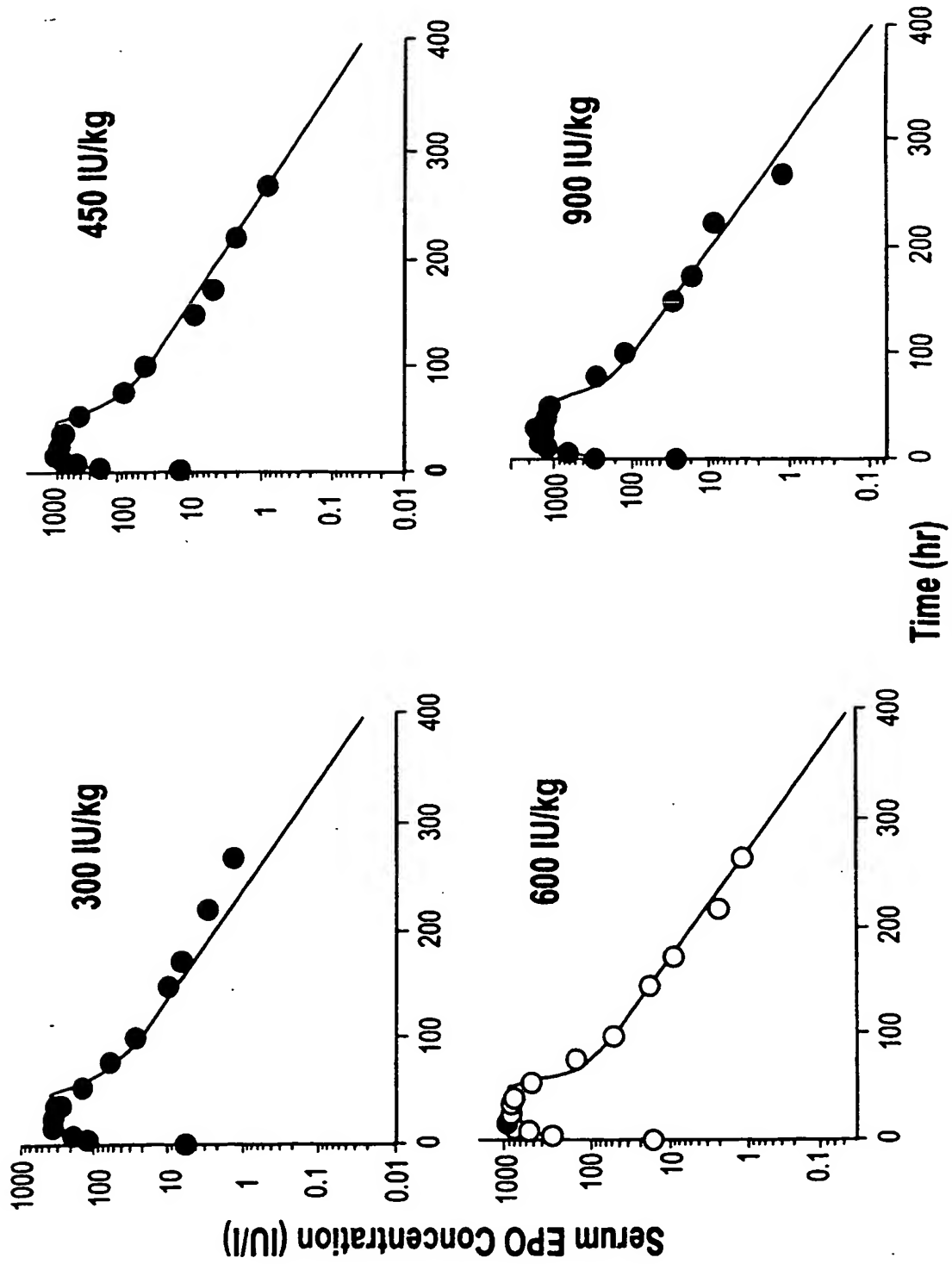
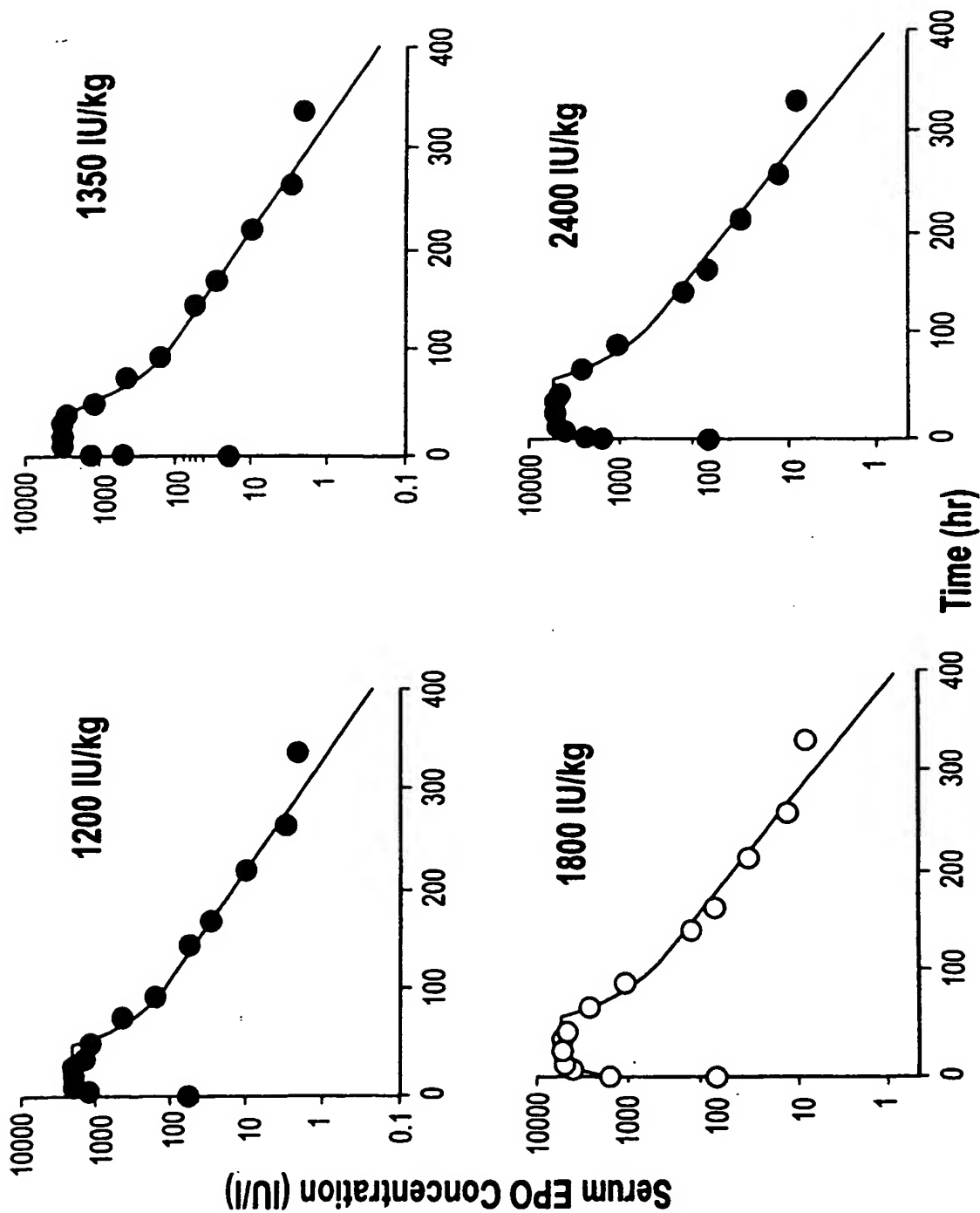


FIG. 4





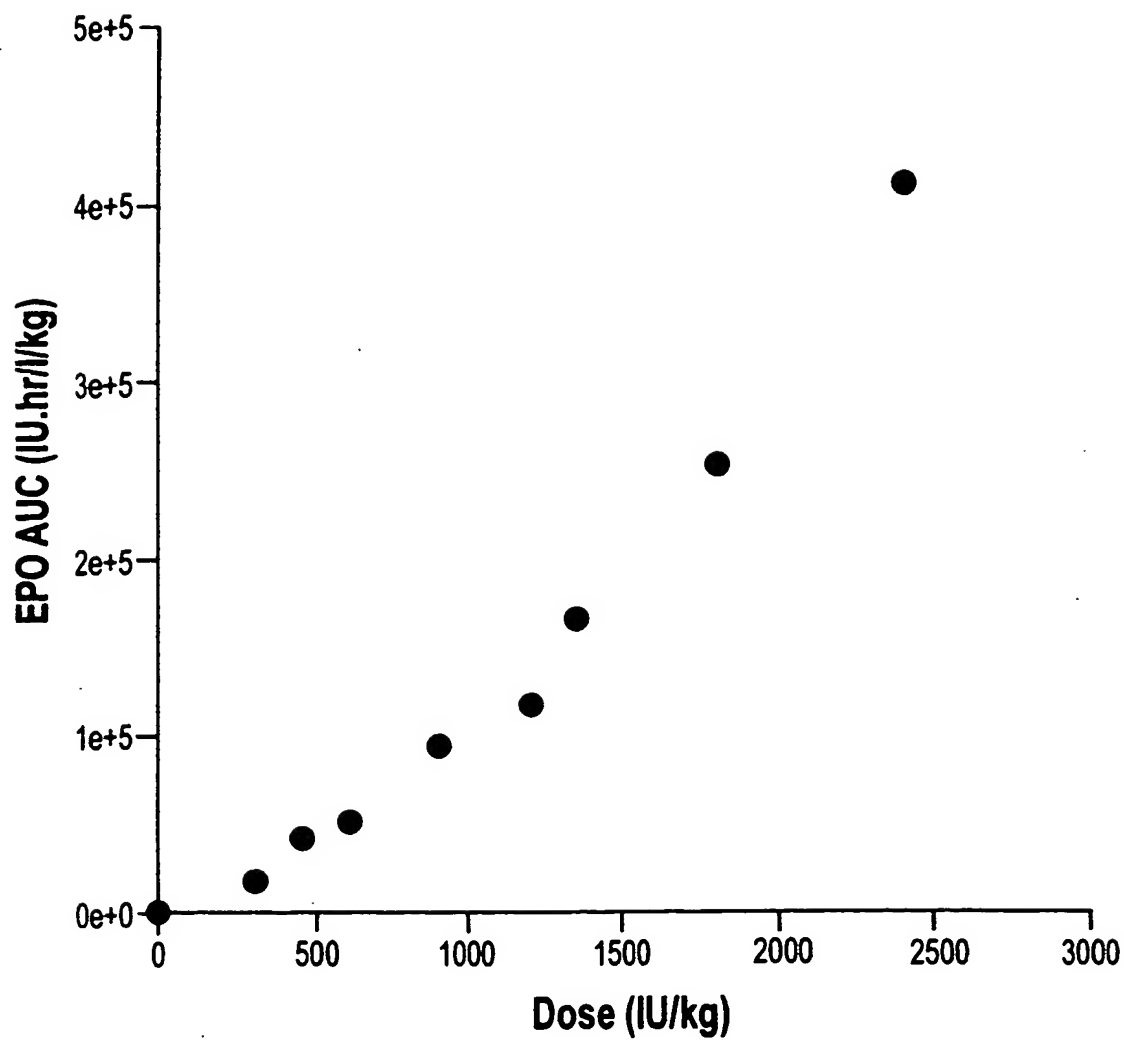


FIG. 6

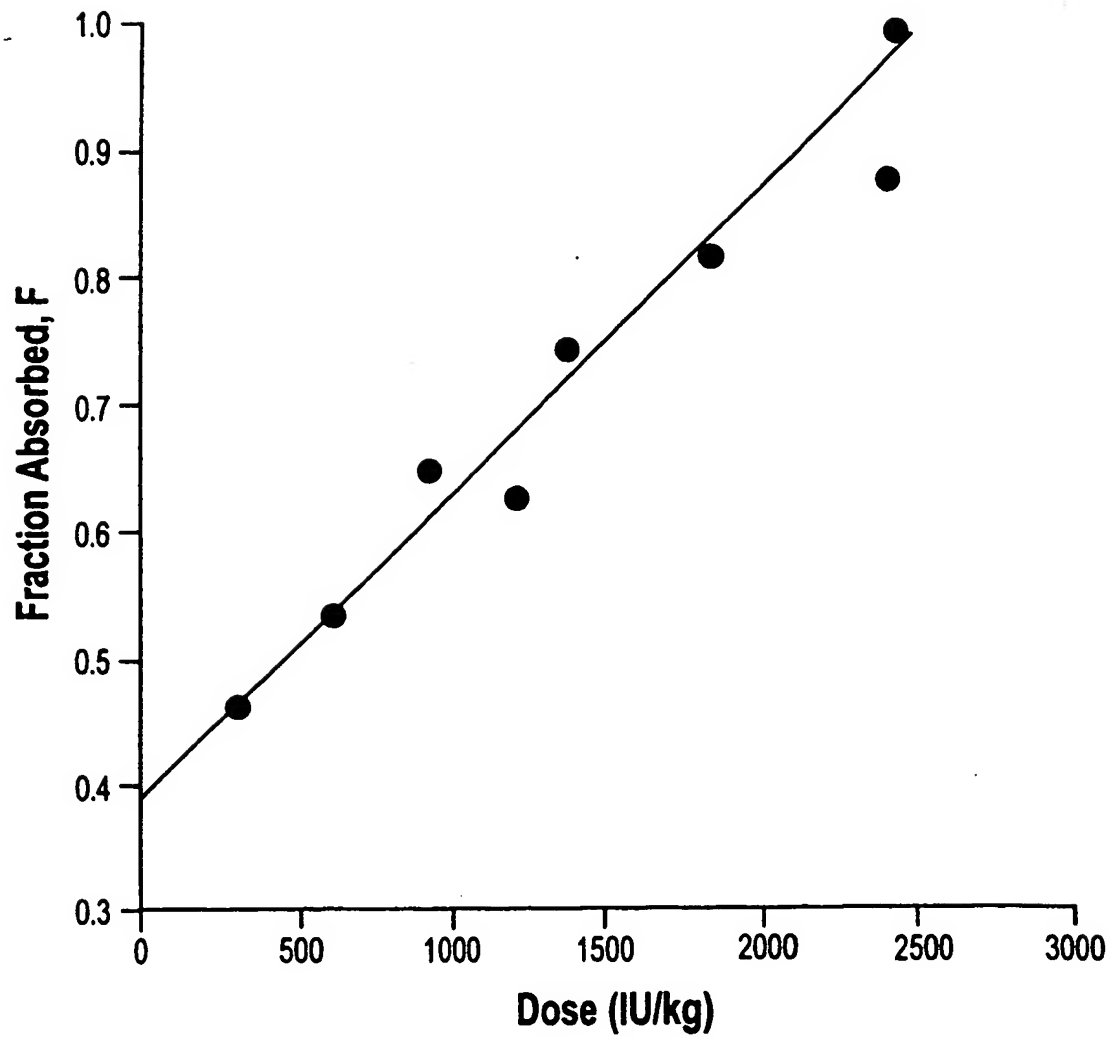


FIG. 7



## BIOAVAILABILITY VALUES FOR SUBCUTANEOUS EPO

DOSE (IU/kg)	F (fitted)	F (linear regression)	F (deconvolution)
300	0.464	0.463	0.36
450	0.614	0.50	0.56
600	0.535	0.538	0.51
900	0.651	0.613	0.61
1200	0.631	0.688	0.57
1350	0.748	0.752	0.73
1800	0.823	0.836	0.83
2400	1.00	0.987	1.00

FIG. 8

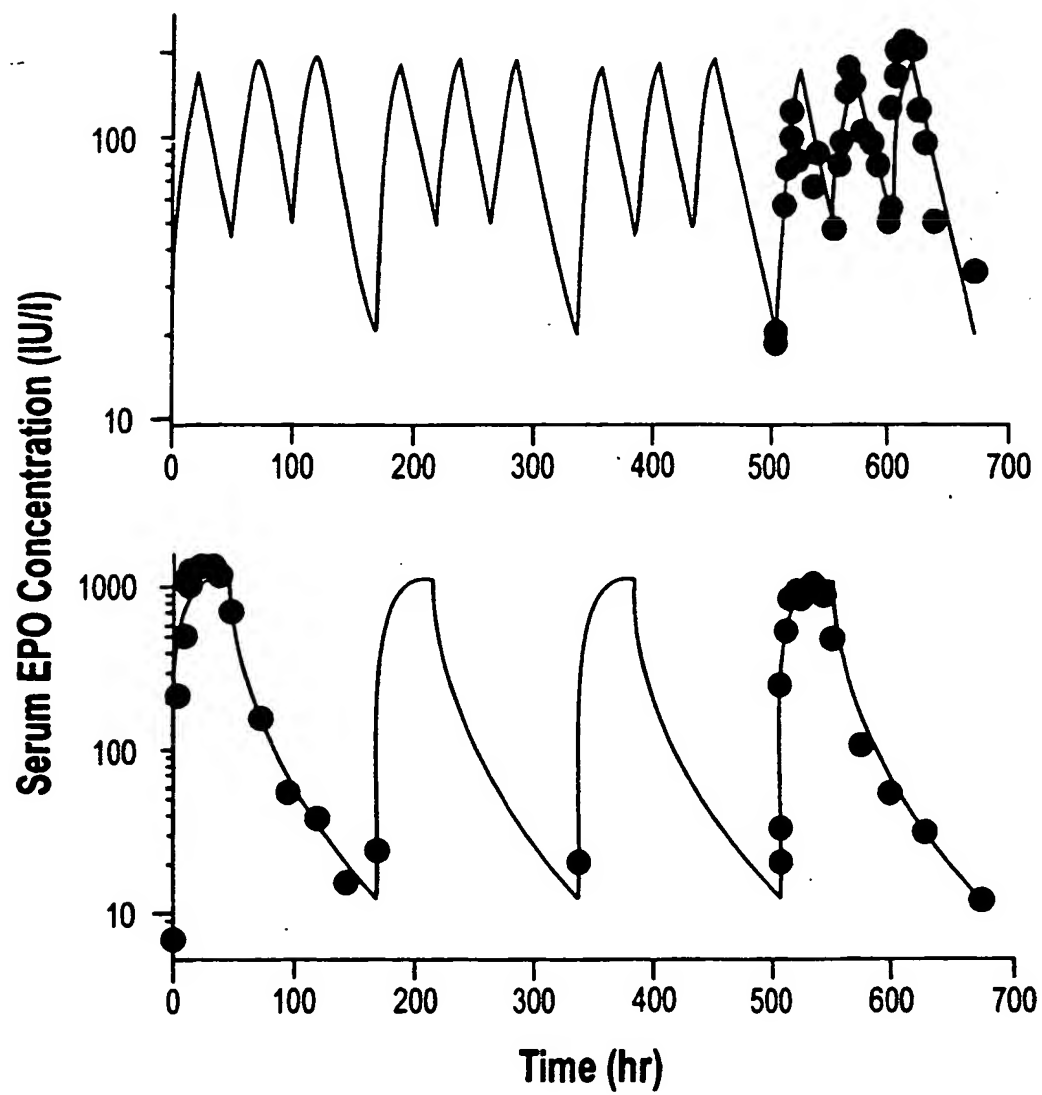


FIG. 9

PHARMACODYNAMIC MODEL

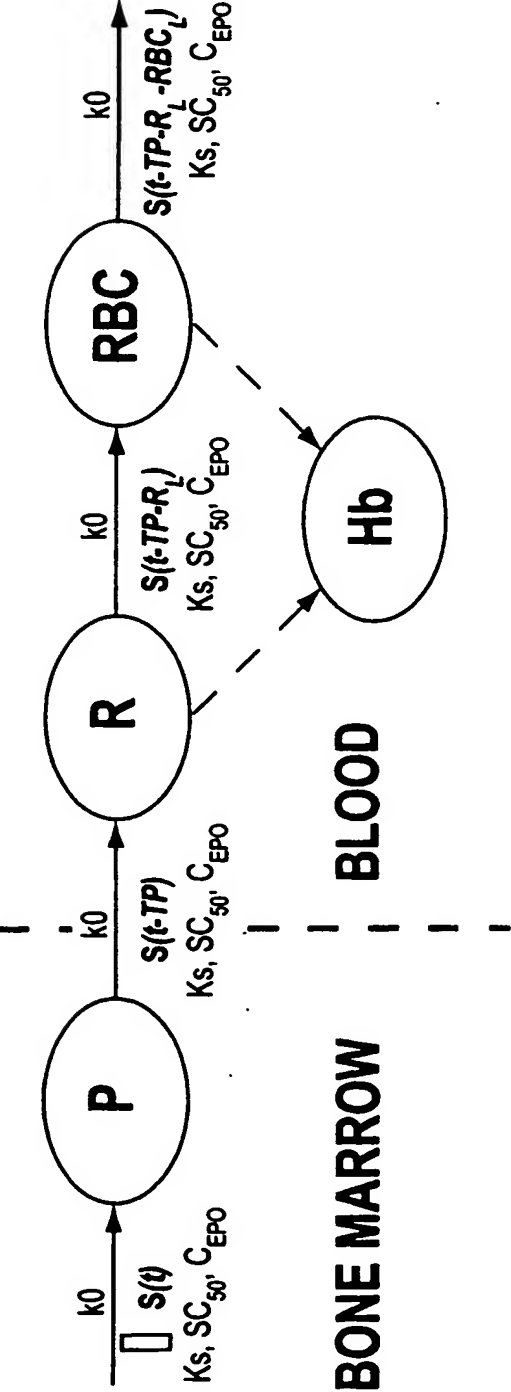
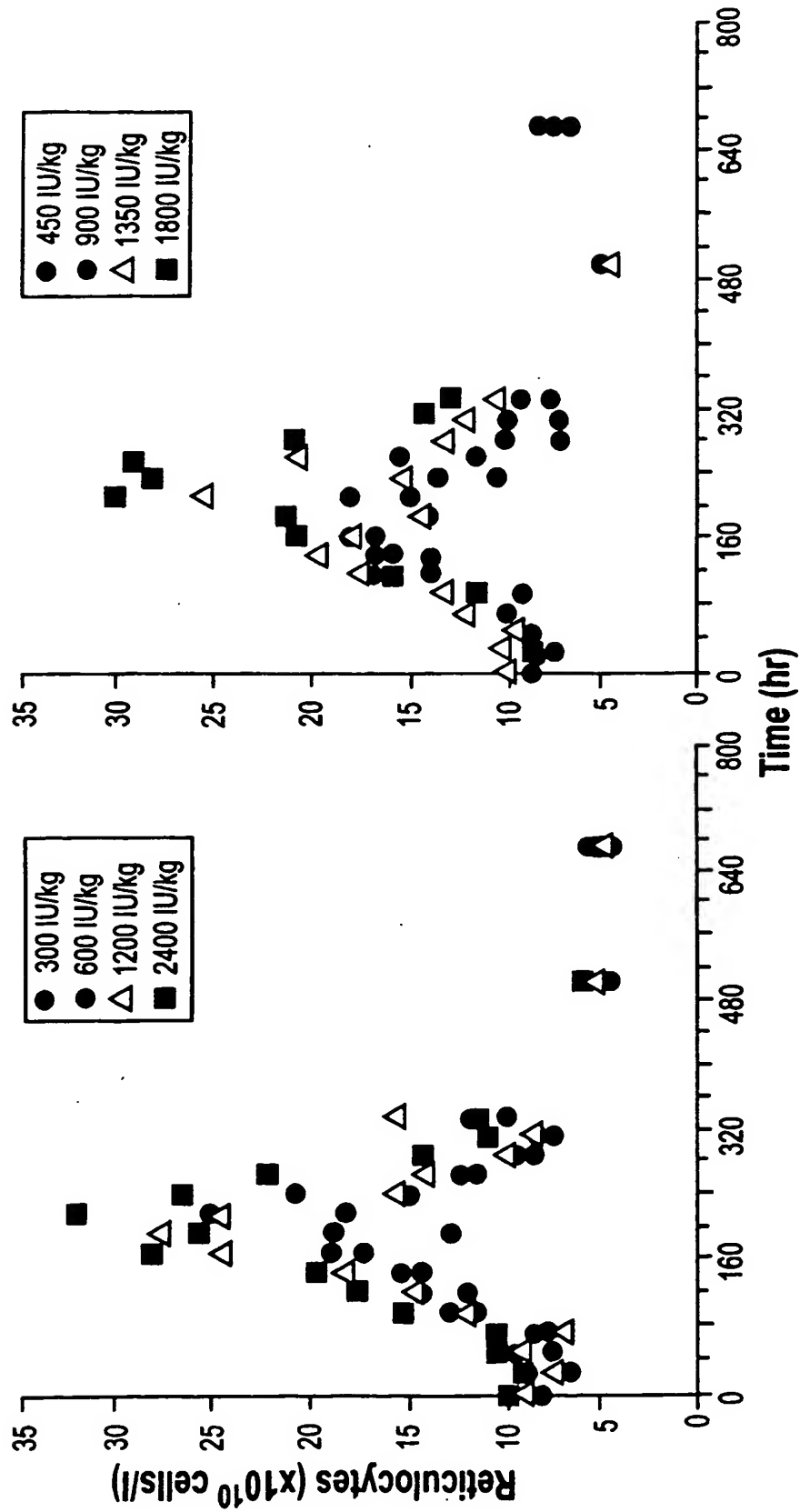


FIG. 10



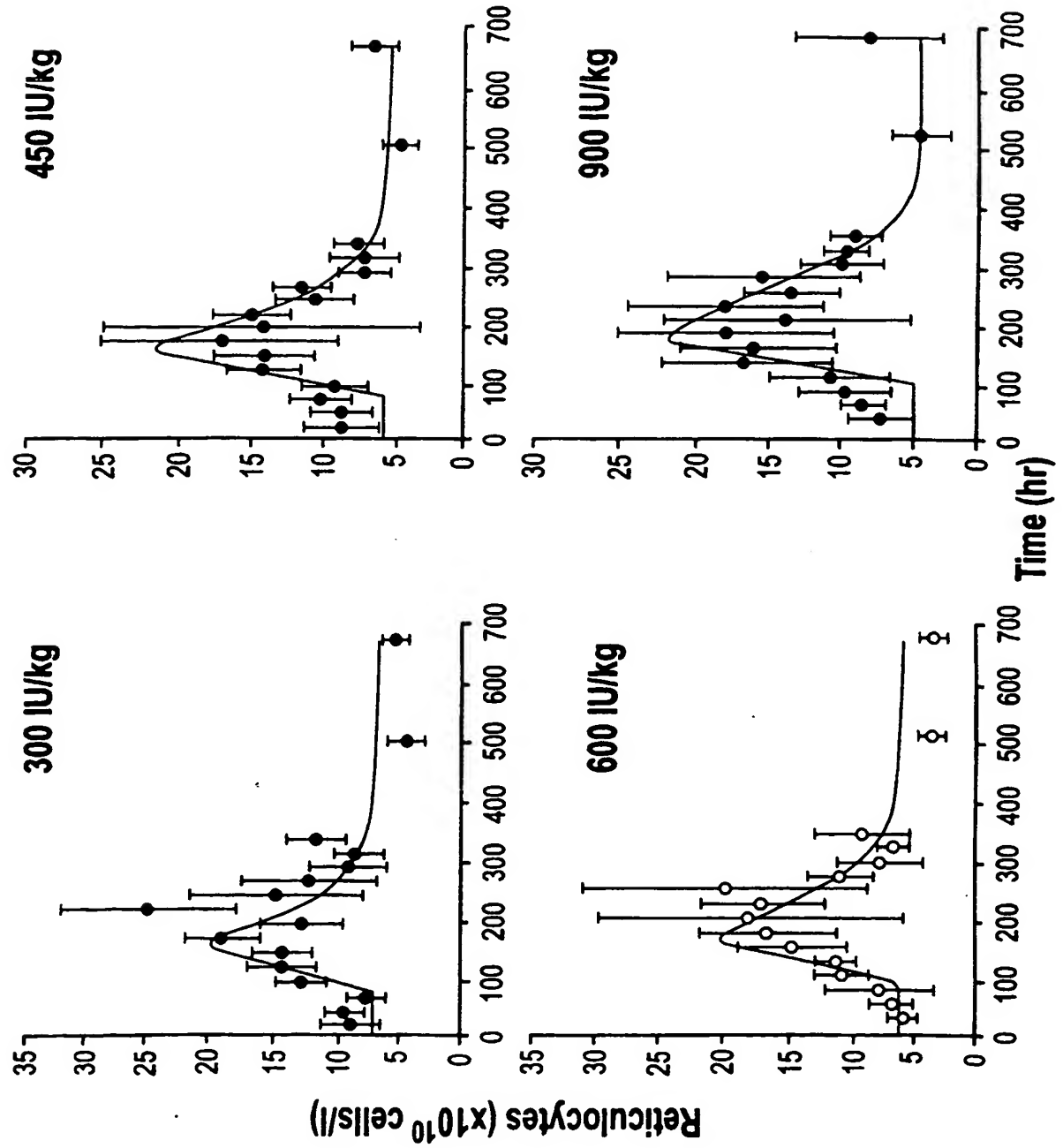


FIG. 12A

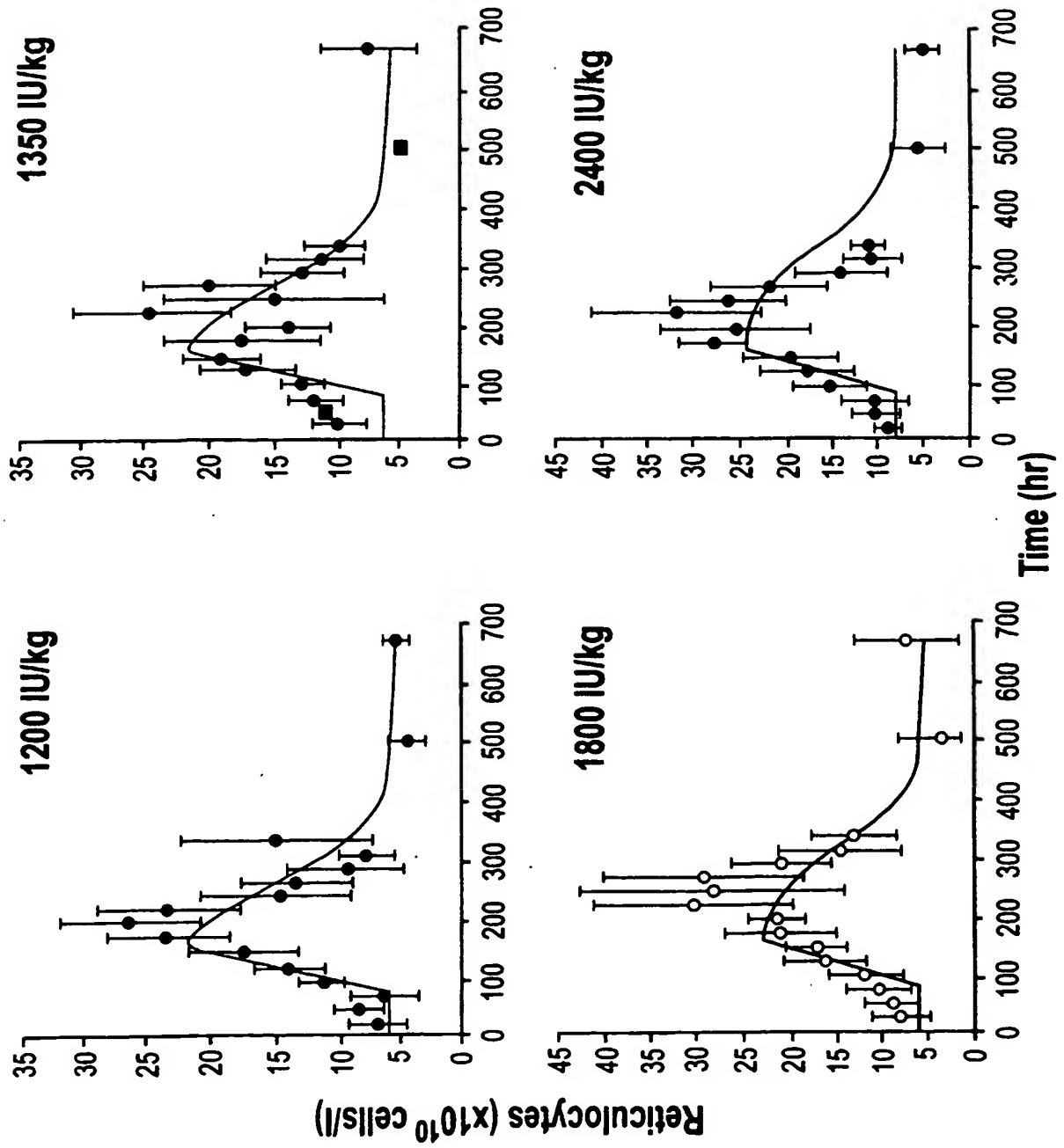


FIG. 12B

## PHARMACODYNAMIC PARAMETERS FOR SUBCUTANEOUS EPO EFFECTS

	PARAMETER	ESTIMATE
ESTIMATED:	Ks (cells/l/hr)	$0.3709 \times 10^{10}$
	SC50 (IU/l)	22.58
	TP (hr)	81.96
FIXED:	$R_L$ (hr)	72
	$RCB_L$ (hr)	2880
	Hb (pg/cell)	29.5
	Threshold (=SC50; IU/l)	22.58

**FIG.13**

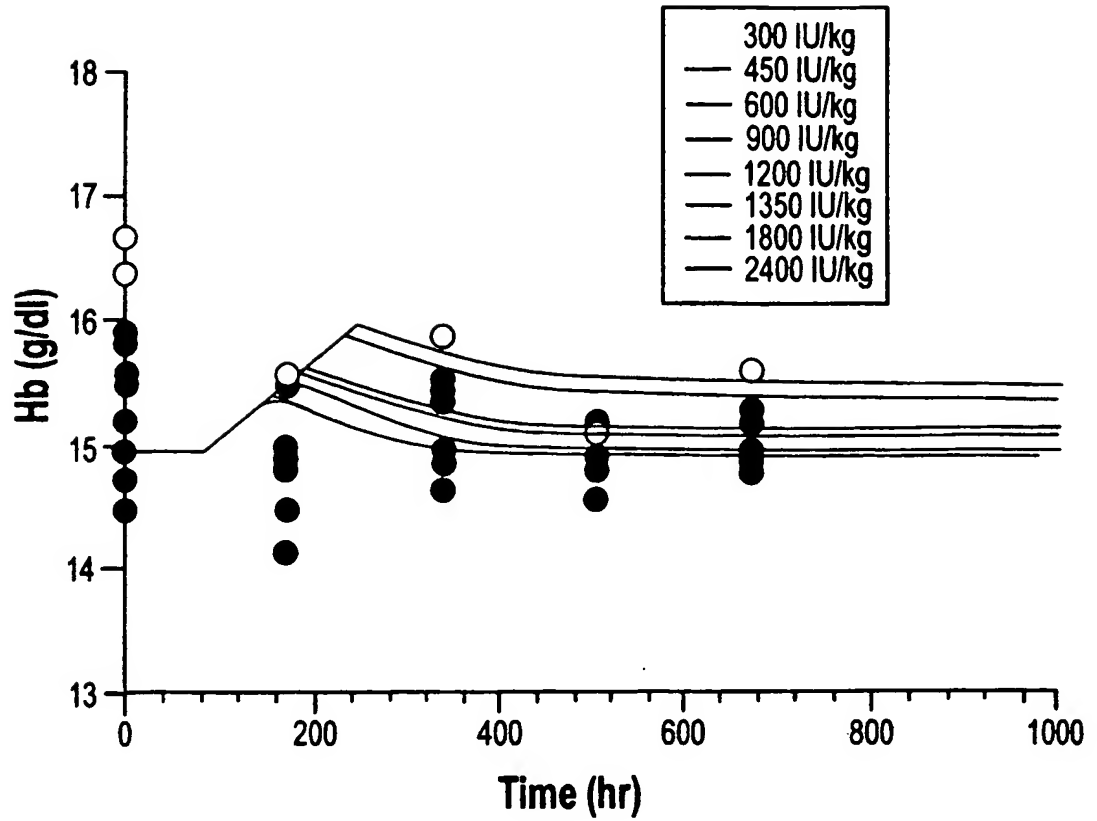


FIG. 14



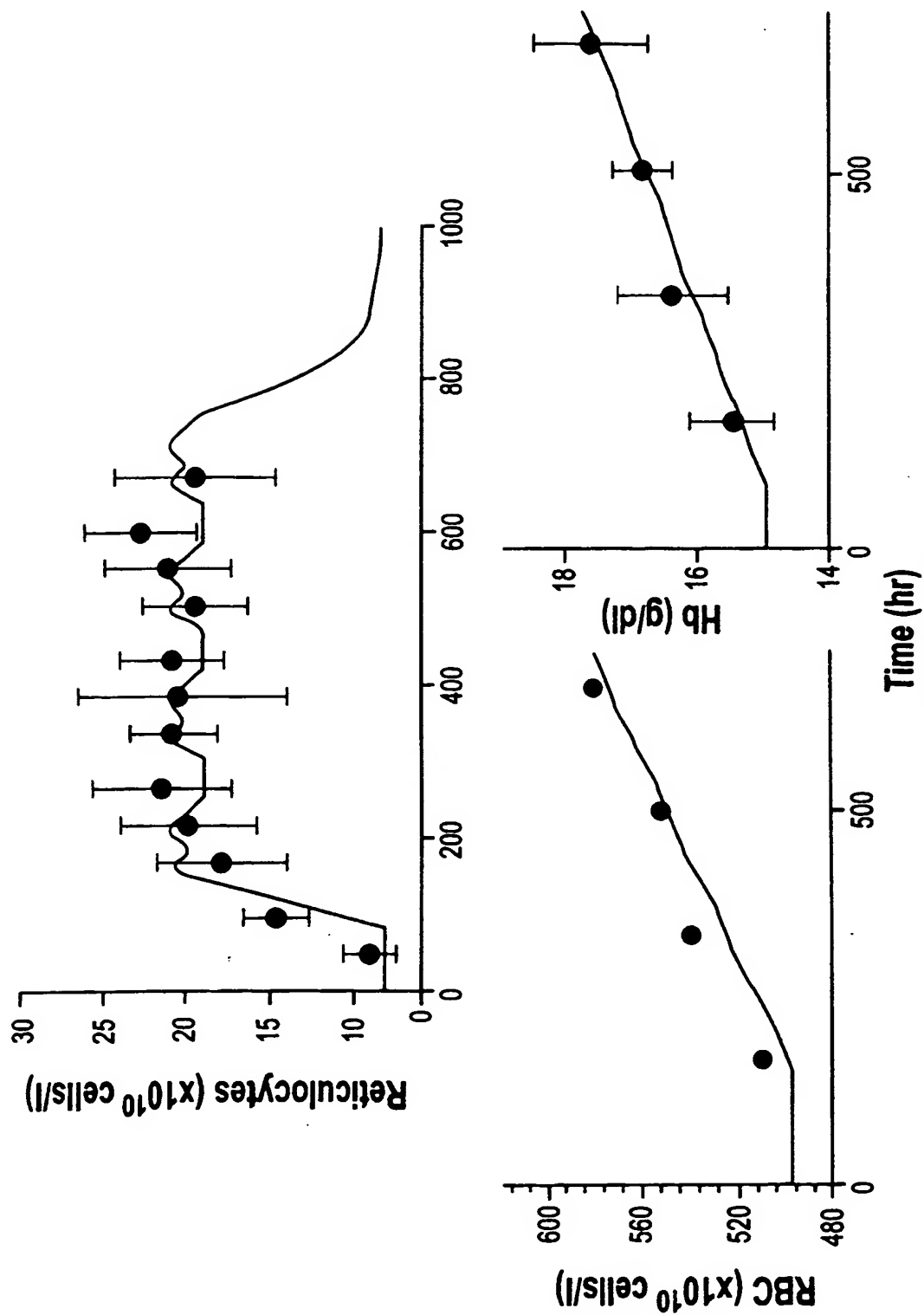


FIG. 15

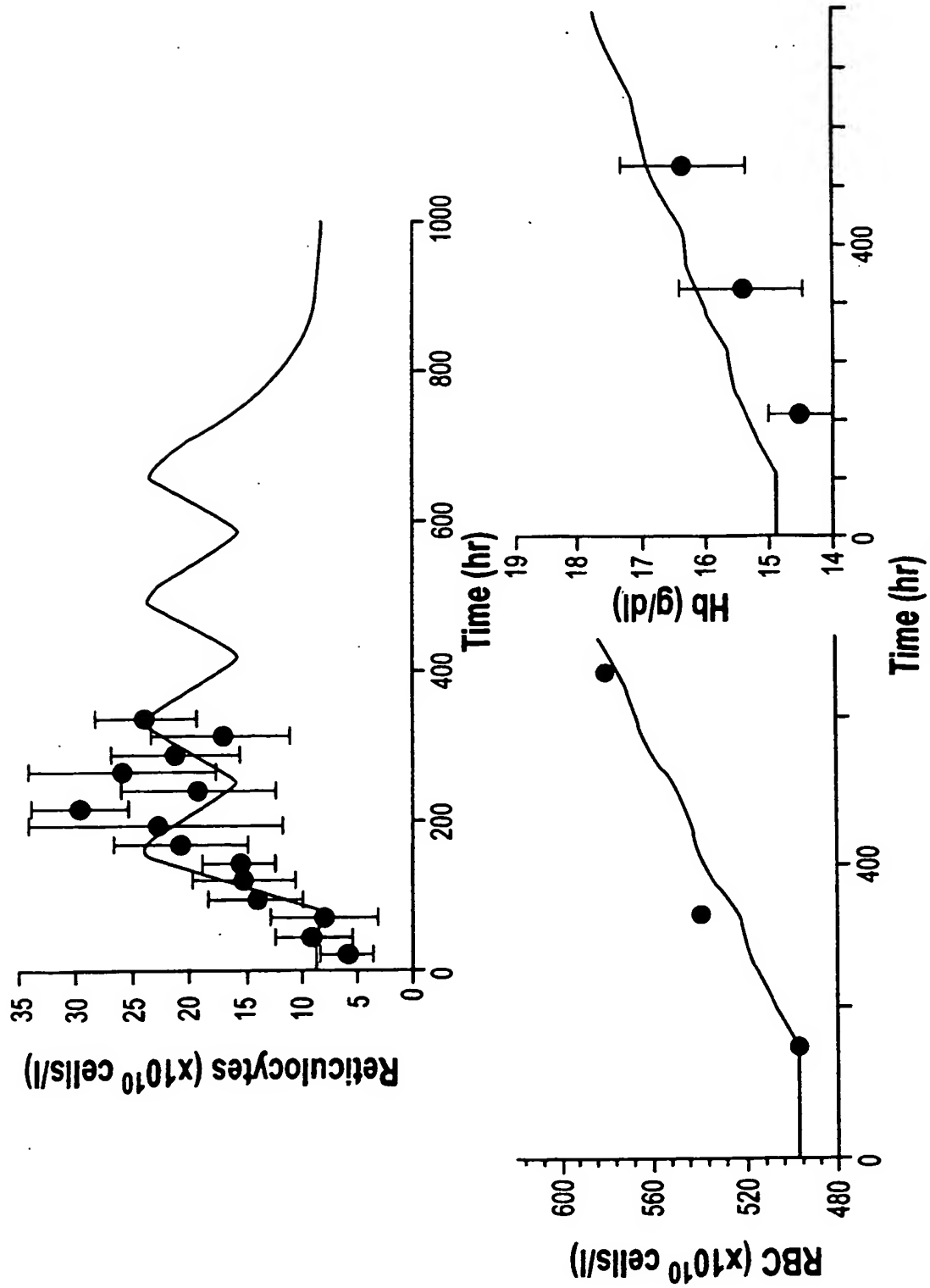


FIG. 16

Study Type/Description	Study Identifier	Ref No.
Pharmacokinetics/Pharmacodynamics Single-center, open-label, parallel design, randomized study conducted in 36 healthy subjects (36 enrolled and analyzed for safety; 34 completed and analyzed for pharmacokinetic and pharmacodynamic [PK/PD]). Subjects were randomized to two treatment groups and received Epoetin alfa as either the standard cancer regimen (150 IU/kg s.c. t.i.w.) or a weekly fixed dose regimen (40,000 IU s.c. q.w.) for 4 wk.	EPO-PHI-373 (Pivotal)	1
Pharmacokinetics/Pharmacodynamics Single-center, open-label, parallel design, randomized study conducted in 49 healthy subjects (49 enrolled and analyzed for safety; 46 completed and analyzed for PK/PD). Subjects were randomized to two treatment groups and received Epoetin alfa as either the standard cancer regimen (150 IU/kg s.c. t.i.w.) or a weekly fixed dose regimen (40,000 IU s.c. q.w.) for 4 wk.	EPO-PHI-370 (Supportive)	2
Pharmacokinetics/Pharmacodynamics Open-label, randomized, placebo controlled, parallel-group, single-center study conducted in 32 subjects (32 enrolled and analyzed for safety; 30 completed and analyzed for PK/PD). Subjects were randomized into three treatment groups (N = 5 each) to receive one of the six treatments (450-, 900-, 1350-, and 1800-IU/kg single s.c. dose, and 150-IU/kg s.c. t.i.w. for 4 wk).	EPO-PHI-358 (Pilot exploratory)	3
Pharmacokinetics/Pharmacodynamics Open-label, randomized, placebo controlled, parallel-group, single-center study conducted in 30 subjects. Subjects were randomized into six treatment groups (N = 5 each) to receive one of the six treatments (300-, 600-, 1200-, and 2400-IU/kg single s.c. dose, and 600-IU/kg s.c. q.w. for 4 wk).	EPO-PHI-359 (Pilot exploratory)	4

FIG. 17

Applicant: The R. W. Johnson Pharmaceutical Research Institute Drug: Epoetin Alfa Once Weekly Dosing NDA No.: Insert NDA No.									
Study No. (Ref No.)	Study Type	Dosage Form(s) Study Design	Dose	Batch No. Plant/Date Manufactured	No. of Subjects	Related IND or NDA No.s	Submission Date	Applicant Conclusion	Previous Agency Responses on Study with Date of Correspondence
RWJPRI Clinical Study EPO-PHI- 373 (1)	s.c.	10,000 IU/ml solution for s.c. injection (Formula FD 22512-000-T-45)	150 IU/kg t.i.w. s.c. administration for 4 wk	10,000 IU/ml formulation: 99KS077 Manufactured at Cilag AG Switzerland in Oct 1999	36 enrolled 34 analyzed	NA	NA	Despite the difference in total exposure of erythropoietin in serum (AUC of Epoetin alfa) after the 150- IU/kg t.i.w. and the 40,000-IU q.w. dosing regimens, the hemoglobin responses to the two regimens were similar.	
		40,000 IU/ml solution for s.c. injection (Formula FD 22512-000-AA- 45)  Single-center, open-label, parallel- design, randomized study in healthy subjects. Two parallel treatment groups: 150 IU/kg s.c. t.i.w. x 4 wk and 40,000 IU q.w. x 4 wk	40,000 IU q.w. s.c. administration for 4 wk	40,000 IU/ml formulation: 99KS091 Manufactured at Cilag AG< Switzerland in Oct 1999					

FIG. 18A

Applicant: The R.W. Johnson Pharmaceutical Research Institute Drug: Epoetin Alfa Once Weekly Dosing NDA No.: Insert NDA No.									
Study No (Ref No.)	Study Type	Dosage Form(s) Study Design	Dose	Batch No. Plant/Date Manufactured	No. of Subjects	Related IND or NDA No.s	Submission Date	Applicant Conclusion	Previous Agency Responses on Study with Date of Correspondence
RWJPRI Clinical Study EPO-PHI- 370 (2)	s.c.	10,000 IU/ml solution for s.c. injection (Formula FD 22512-000-C-45)	150 IU/kg t.i.w. s.c. administration for 4 wk	10,000 IU/ml formulation: Lot D000123 Manufactured at Amgen Inc., Thousand Oaks, CA	49 enrolled 46 analyzed	IND BB- IND- 2318	Protocol 01 Jul 1999 Amended Protocols	Despite the difference in total exposure of erythropoietin in serum (AUC of Epoetin alfa) after the 150- IU/kg t.i.w. and the 40,000-IU q.w. dosing regimens, the hemoglobin responses to the two regimens were similar.	
		40,000 IU/ml solution for s.c. injection (Formula FD 22512-000-AC- 45)  Single-center, open-label, parallel- design, randomized study in healthy subjects. Two parallel treatment groups: 150 IU/kg s.c. t.i.w. x 4 wk and 40,000 IU q.w. x 4 wk.	40,000 IU q.w. s.c. administration for 4 wk	40,000 IU/ml formulation: Lot D000175 Manufactured at Amgen Inc., Thousand Oaks, CA					

FIG. 18B

The R.W. Johnson Pharmaceutical Research Institute										
Epoetin Alfa Once Weekly Dosing										
Insert NDA No.										
Applicant: Drug: NDA No.:	Study No (Ref No.)	Study Type	Dosage Form(s) Study Design	Dose	Batch No. Plant/Date Manufactured	No. of Subjects	Related IND or NDA No.s	Submission Date	Applicant Conclusion	Previous Agency Responses on Study with Date of Correspondence
	RWJPRI Clinical Study EPO-PHI- 358 (3)	s.c.	40,000 IU/ml solution for s.c. administration (Formula FD 22512-000-J-45)	Single s.c. dose: 450, 900, 1350, 1800 IU/kg  Multiple s.c. dose: 150 IU/kg t.i.w. for 4 wk	5C903J, Manufactured at Hoffman La- Roche, Basel Switzerland; March 1995	32 enrolled  30 analyzed	IND BB- IND-2318	Protocol 06 May 1996  Amended Protocol 06 May 1996	Pharmacological response to Epoetin alfa is a function of dose and dosing regimen. The absorption rate of Epoetin alfa after subcutaneous administration was independent of dose. Clearance of Epoetin alfa was dose- dependent - it decreased with increasing dose. There was an increasing trend of AUC of reticulocytes with AUC of Epoetin alfa for single doses. A continuous pharmacological response (a continuous production of reticulocytes and sustained elevation of	

FIG. 18C

1/2

Applicant: The R.W. Johnson Pharmaceutical Research Institute									
Drug: Epoetin Alfa Once Weekly Dosing									
NDA No.: Insert NDA No.									
Study No. (Ref No.)	Study Type	Dosage Form(s) Study Design	Dose	Batch No. Plant/Date Manufactured	No. of Subjects	Related IND or NDA No.s	Submission Date	Applicant Conclusion	Previous Agency Responses on Study with Date of Correspondence
		groups (N = 5 each) to receive one of the six treatments (placebo 450, 900, 1350, and 1800 IU/kg single dose, and 150 IU/kg t.i.w. for 4 wk).						hemoglobin) requires Epoetin alfa serum concentration to be maintained continuously (such as after 150 IU/kg t.i.w. dosing regimen) or intermittently (such as after the 600-IU/kg q.w. dosing regimen) above endogenous level.	

1/2

FIG. 18C

Applicant: The R.W. Johnson Pharmaceutical Research Institute									
Drug: Epoetin Alfa Once Weekly Dosing									
NDA No.: Insert NDA No.									
Study No (Ref No.)	Study Type	Dosage Form(s) Study Design	Dose	Batch No. Plant/Date Manufactured	No. of Subjects	Related IND or NDA No.s	Submission Date	Applicant Conclusion	Previous Agency Responses on Study with Date of Correspondence
RWJPRI Clinical Study EPO-PHI- 359 (4)	s.c.	40,000 IU/ml solution for s.c. administration (Formula FD- 22512-000-J-45)	Single s.c. dose: 300, 600, 1200, 2400 IU/kg  Multiple s.c. doses: 600 IU/kg q.w. for 4 wk	5C903J, Manufactured at Hoffman La- Roche, Basel Switzerland; March 1995	30 enrolled  30 analyzed	IND BB- IND-2318	06 May 1996	Pharmacological response to Epoetin alfa is a function of dose and dosing regimen. The absorption rate of Epoetin alfa after subcutaneous administration was independent of dose. Clearance of Epoetin alfa was dose- dependent - it decreased with increasing dose. There was an increasing trend of AUC of reticulocytes with AUC of Epoetin alfa for single doses. A continuous pharmacological response (a continuous production of reticulocytes and sustained elevation of	
		Open-label, randomized, placebo controlled, parallel-group, single center study conducted in healthy subjects. Subjects were randomized into six treatment groups (N = 5 each) to receive one of the six treatments (placebo 300							

FIG. 18D



Applicant: The R.W. Johnson Pharmaceutical Research Institute Drug: Epoetin Alfa Once Weekly Dosing NDA No.: Insert NDA No.									
Study No. (Ref No.)	Study Type	Dosage Form(s) Study Design	Dose	Batch No. Plant/Date Manufactured	No. of Subjects	Related IND or NDA No.s	Submission Date	Applicant Conclusion	Previous Agency Responses on Study with Date of Correspondence
		600, 1200, 2400 IU/kg and 600 IU/kg q.w. for 4 wk).						hemoglobin) requires Epoetin alfa serum concentration to be maintained continuously (such as after 150 IU/kg t.i.w. dosing regimen) or intermittently (such as after the 600-IU/kg q.w. dosing regimen) above endogenous level.	

FIG. 18D

Applicant: The R.W. Johnson Pharmaceutical Research Institute Drug: Epoetin Alfa Once Weekly Dosing NDA No.: Insert NDA No.						
Study	Dose	C <sub>max</sub> (mIU/mL)	t <sub>max</sub> (h)	AUC <sup>a</sup> (mIU·h/mL)	CL/F (mL/h/kg)	t <sub>1/2</sub> (h)
Single Subcutaneous Dose Administration						
EPO359	300 IU/kg	429 ± 86 (20.0%)	22.8 ± 8.1 (36.5%)	20056 ± 4138 (20.6%)	15.5 ± 3.1 (20.2%)	68.2 ± 52.2 (76.6%)
EPO358	450 IU/kg	1263 ± 290 (23.0%)	15.6 ± 5.8 (37.0%)	45498 ± 12342 (27.1%)	10.4 ± 2.6 (24.9%)	24.2 ± 3.2 (13.2%)
EPO359	600 IU/kg	1263 ± 486 (38.5%)	27.6 ± 9.1 (33.0%)	55475 ± 16384 (29.5%)	11.8 ± 4.2 (35.5%)	29.3 ± 9.4 (32.0%)
EPO358	900 IU/kg	2235 ± 599 (26.8%)	22.2 ± 12.7 (57.0%)	103154 ± 28024 (27.2%)	9.36 ± 2.97 (31.7%)	36.0 ± 13.5 (37.3%)
EPO359	1200 IU/kg	2256 ± 710 (31.4%)	26.4 ± 7.8 (29.4%)	119932 ± 44217 (36.9%)	11.2 ± 4.2 (37.7%)	78.5 ± 95.4 (122%)
EPO358	1350 IU/kg	3755 ± 879 (23.4%)	23.4 ± 8.8 (37.8%)	174193 ± 41417 (23.8%)	8.23 ± 2.57 (31.3%)	33.4 ± 2.4 (7.2%)
EPO358	1800 IU/kg	4370 ± 1673 (38.3%)	28.8 ± 7.8 (27.2%)	258600 ± 101175 (39.1%)	7.64 ± 2.22 (29.1%)	32.4 ± 8.4 (25.9%)
EPO359	2400 IU/kg	6819 ± 764 (11.2%)	25.2 ± 6.2 (24.7%)	429441 ± 32139 (7.5%)	5.61 ± 0.44 (7.8%)	43.6 ± 25.9 (59.5%)
Multiple Subcutaneous Dose Administration						
EPO358 Wk 4	150 IU/kg t.i.w.	252 ± 71 (28.0%)	NA	16582 ± 4256 (25.7%)	28.7 ± 7.8 (27.1%)	25.9 ± 7.1 (27.2%)
EPO359 Wk 1	600 IU/kg q.w.	1502 ± 384 (25.6%)	21.6 ± 6.1 (28.5%)	63439 ± 10893 (17.2%)	9.70 ± 1.8 (18.1%)	28.3 ± 7.5 (26.3%)
EPO359 Wk 4	600 IU/kg q.w.	1278 ± 213 (16.6%)	24.0 ± 8.7 (36.4%)	50725 ± 6774 (13.4%)	12.0 ± 1.6 (13.2%)	28.1 ± 7.0 (24.9%)

FIG. 19

11  
21

The R.W. Johnson Pharmaceutical Research Institute						
Epoetin Alfa Once Weekly Dosing						
Insert NDA No.						
Study	Dose	C <sub>max</sub> (mIU/mL)	t <sub>max</sub> (h)	AUC <sup>a</sup> (mIU·h/mL)	CL/F (mL/h/kg)	t <sub>1/2</sub> (h)
Single Subcutaneous Dose Administration						
EPO370 Wk 4	150 IU/kg i.w.	191 ± 100 (52.3%)	NA	13446 ± 4374 (32.5%)	37.1 ± 12.3 (33.1%)	31.8 ± 13.4 (42.1%)
EPO370 Wk 4	40,000 IU q.w.	785 ± 427 (54.4% <sup>0</sup> )	18 ± 5 (29.4%)	30084 ± 13516 (44.9%)	23.2 ± 10.8 (46.5%)	39.3 ± 7.1 (18.1%)
EPO373 Wk 4	150 IU/kg i.w.	143 ± 54 (37.8%)	NA	8587 ± 1521 (17.7%)	54.1 ± 10.1 (18.7%)	19.4 ± 8.1 (41.5%)
EPO373 Wk 4	40,000 IU q.w.	861 ± 445 (51.7%)	16 ± 8 (45.6%)	25747 ± 9062 (35.2%)	24.7 ± 7.2 (29.1%)	15.0 ± 6.1 (40.9%)

<sup>a</sup> AUC(0-168h) during a dose week for multiple dose regimens and AUC(0-672h) during the 4-wk of study period for single doses.

NA = Not applicable

FIG. 19

1/2

Applicant:		The R.W. Johnson Pharmaceutical Research Institute		
Drug:		Epoetin Alfa Once Weekly Dosing		
NDA No.:		Insert NDA No.		
Study No. Primary Supportive (Ref. No.)	Type of Biological Fluid	Analysis Method	Sensitivity of Method Range (mU/mL)	Specificity of Assay
EPO-PHI-358 Pilot /Exploratory	Serum	RIA (RWJPRI) <sup>23</sup>	7.8-125	Detects both endogenous and exogenous EPO
EPO-PHI-359 Pilot /Exploratory	Serum	RIA (RWJPRI) <sup>23</sup>	7.8-125	Detects both endogenous and exogenous EPO
EPO-PHI-370 Supportive	Serum	RIA (PPD) <sup>24</sup>	7.8-125	Detects both endogenous and exogenous EPO
EPO-PHI-373 Pivotal	Serum	ELISA (PPD) <sup>25</sup>	7.8-125	Detects both endogenous and exogenous EPO

FIG. 20

**Mean  $\pm$  SD Demographic and Baseline Parameters  
for Subjects Enrolled in Clinical  
Studies EPO-PHI-358 and EPO-PHI-359**

Parameter	EPO-PHI-358 (N=32)	EPO-PHI-359 (N=30)
Age (yr)	35.7 $\pm$ 7.25	34.1 $\pm$ 6.76
Weight (kg)	76.7 $\pm$ 7.10	77.7 $\pm$ 8.83
Height (cm)	174.2 $\pm$ 7.69	174.7 $\pm$ 7.88
Race		
White	8 (25%)	9 (30%)
Black	4 (13%)	1 (3%)
Asian	0 (0%)	1 (3%)
Hispanic	20 (63%)	19 (63%)

**FIG. 21**

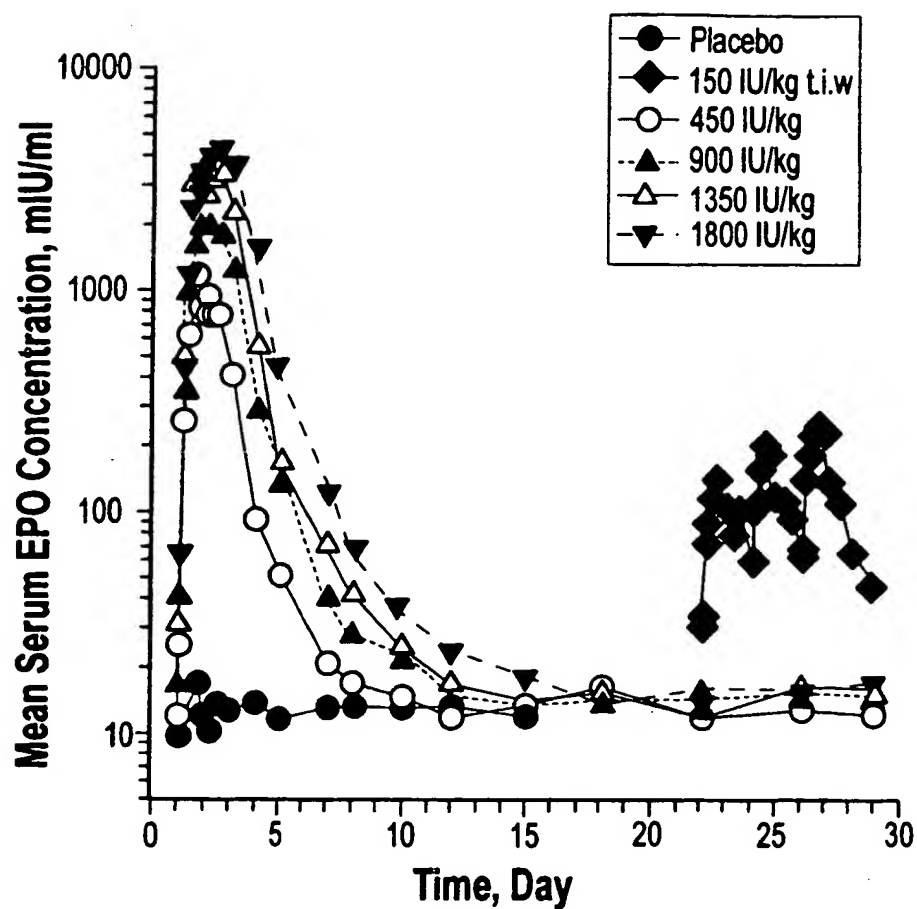


FIG. 22

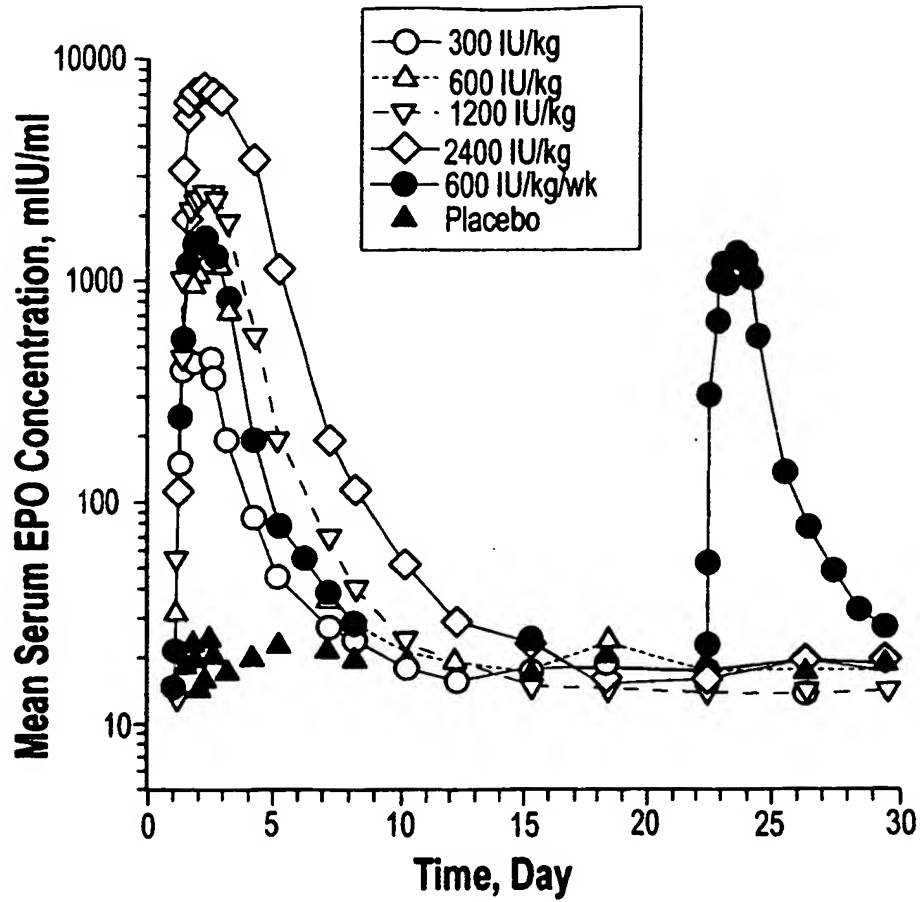


FIG. 23

**Mean  $\pm$  SD (%CV) Pharmacokinetic and Pharmacodynamic Parameters (Clinical Studies EPO-PHI-358 and EPO-PHI-359)**

Study	Dose	C <sub>max</sub> (mIU/mL)	t <sub>max</sub> (h)	AUC <sup>a</sup> (mIU·h/mL)	CL/F (mL/h/kg)	t <sub>1/2</sub> (h)	%RET <sup>b</sup> AUC (%·h)
EPO359	300 IU/kg	429 $\pm$ 86 (20.0%)	22.2 $\pm$ 8.1 (36.5%)	20056 $\pm$ 4138 (20.6%)	15.5 $\pm$ 3.1 (20.2%)	68.2 $\pm$ 52.2 (76.6%)	1280 $\pm$ 157 (12.3%)
EPO358	450 IU/kg	1263 $\pm$ 290 (23.0%)	15.6 $\pm$ 5.8 (37.0%)	45498 $\pm$ 12342 (27.1%)	10.4 $\pm$ 2.6 (24.9%)	24.2 $\pm$ 3.2 (13.2%)	1191 $\pm$ 164 (13.8%)
EPO359	600 IU/kg	1263 $\pm$ 486 (38.5%)	27.6 $\pm$ 9.1 (33.0%)	55475 $\pm$ 16384 (29.5%)	11.8 $\pm$ 4.2 (35.5%)	29.3 $\pm$ 9.4 (32.0%)	1224 $\pm$ 227 (18.5%)
EPO358	900 IU/kg	2235 $\pm$ 599 (26.8%)	22.2 $\pm$ 12.7 (57.0%)	103154 $\pm$ 28024 (27.2%)	9.36 $\pm$ 2.97 (31.7%)	36.0 $\pm$ 13.5 (37.3%)	1296 $\pm$ 274 (21.1%)
EPO359	1200 IU/kg	2256 $\pm$ 710 (31.4%)	26.4 $\pm$ 7.8 (29.4%)	119932 $\pm$ 44217 (36.9%)	11.2 $\pm$ 4.2 (37.7%)	78.5 $\pm$ 95.4 (122%)	1413 $\pm$ 315 (22.3%)
EPO358	1350 IU/kg	3755 $\pm$ 879 (23.4%)	23.4 $\pm$ 8.8 (37.8%)	174193 $\pm$ 41417 (23.8%)	8.23 $\pm$ 2.57 (31.3%)	33.4 $\pm$ 2.4 (7.2%)	1406 $\pm$ 146 (10.4%)
EPO358	1800 IU/kg	4370 $\pm$ 1673 (38.3%)	28.8 $\pm$ 7.8 (27.2%)	258600 $\pm$ 101175 (39.1%)	7.64 $\pm$ 2.22 (29.1%)	32.4 $\pm$ 8.4 (25.9%)	1679 $\pm$ 407 (24.2%)
EPO359	2400 IU/kg	6819 $\pm$ 764 (11.2%)	25.2 $\pm$ 6.2 (24.7%)	429441 $\pm$ 32139 (7.5%)	5.61 $\pm$ 0.44 (7.8%)	43.6 $\pm$ 25.9 (59.5%)	1720 $\pm$ 233 (13.5%)
EPO358 Wk 4	150 IU/kg i.v.	252 $\pm$ 71 (28.0%)	NA	16582 $\pm$ 4256 (25.7%)	28.7 $\pm$ 7.8 (27.1%)	25.9 $\pm$ 7.1 (27.2%)	

**FIG. 24**

$\frac{1}{2}$



**Mean  $\pm$  SD (%CV) Pharmacokinetic and Pharmacodynamic Parameters (Clinical Studies EPO-PHI-358 and EPO-PHI-359)**

Study	Dose	C <sub>max</sub> (mIU/mL)	t <sub>max</sub> (h)	AUC <sup>a</sup> (mIU·h/mL)	CL/F (mL/h/kg)	t <sub>1/2</sub> (h)	%RET <sup>b</sup> AUC (%·h)
EPO358 Wk 1-4	150 IU/kg t.i.w.						1749 $\pm$ 406 (23.2%)
EPO359 Wk 1	600 IU/kg/wk	1502 $\pm$ 384 (25.6%)	21.6 $\pm$ 6.1 (28.5%)	63439 $\pm$ 10893 (17.2%)	9.70 $\pm$ 1.8 (18.1%)	28.3 $\pm$ 7.5 (26.3%)	
EPO359 Wk 4	600 IU/kg/wk	1278 $\pm$ 213 (16.6%)	24.0 $\pm$ 8.7 (36.4%)	50725 $\pm$ 6774 (13.4%)	12.0 $\pm$ 1.6 (13.2%)	28.1 $\pm$ 7.0 (24.9%)	
EPO359 Wk 1-4	600 IU/kg/wk						2220 $\pm$ 493 (22.2%)

<sup>a</sup> AUC(0-168) during a dosing week for multiple dose regimens and AUC(0-672) during the 4 wk of study period for single doses.

<sup>b</sup> Percent reticulocyte AUC from time-zero to Day 29 after initiation of drug administration.

NA = not applicable

FIG. 24

$\frac{1}{2}$

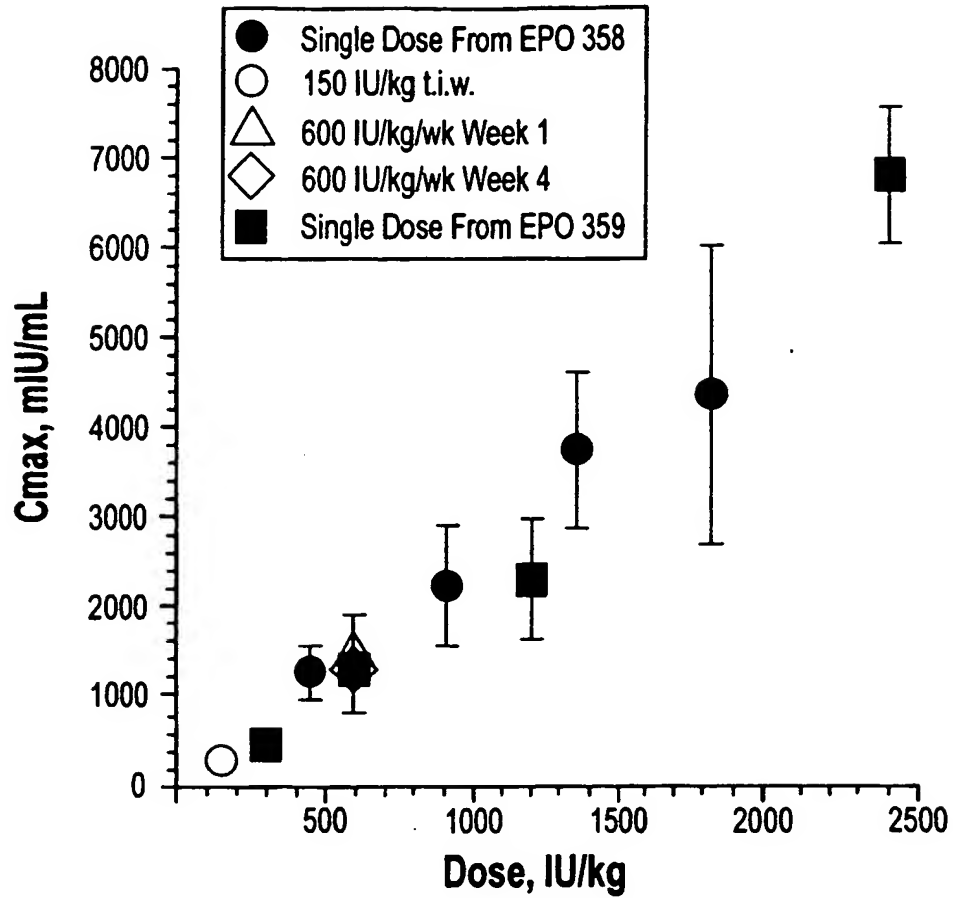


FIG. 25

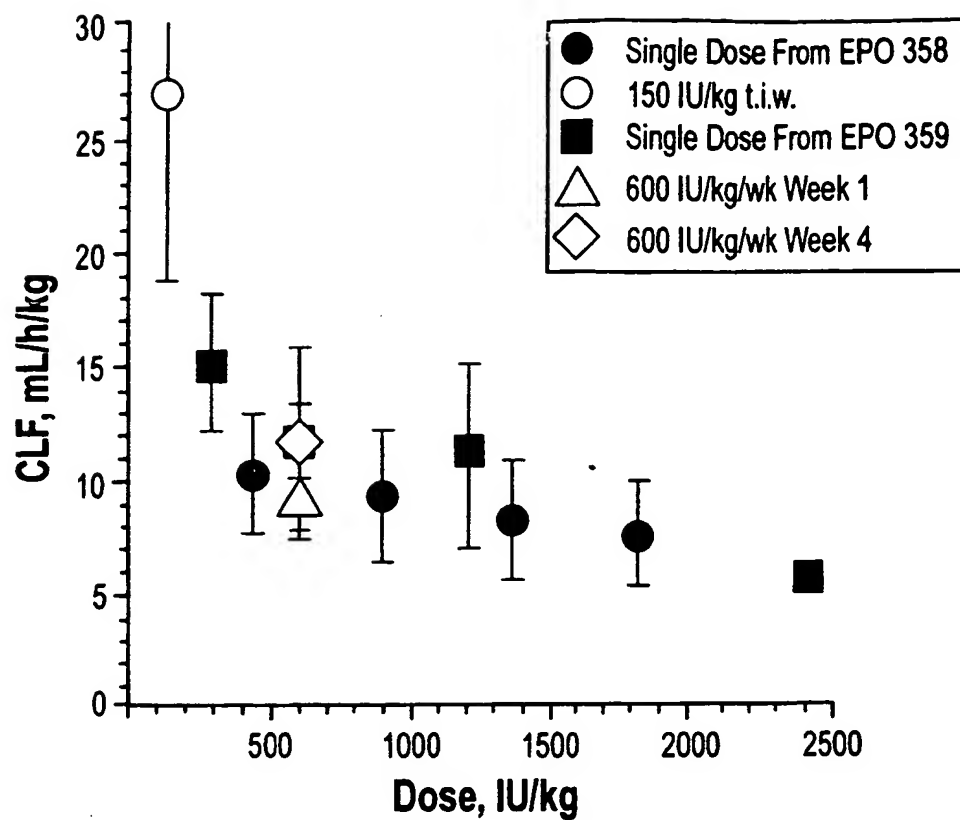


FIG. 26

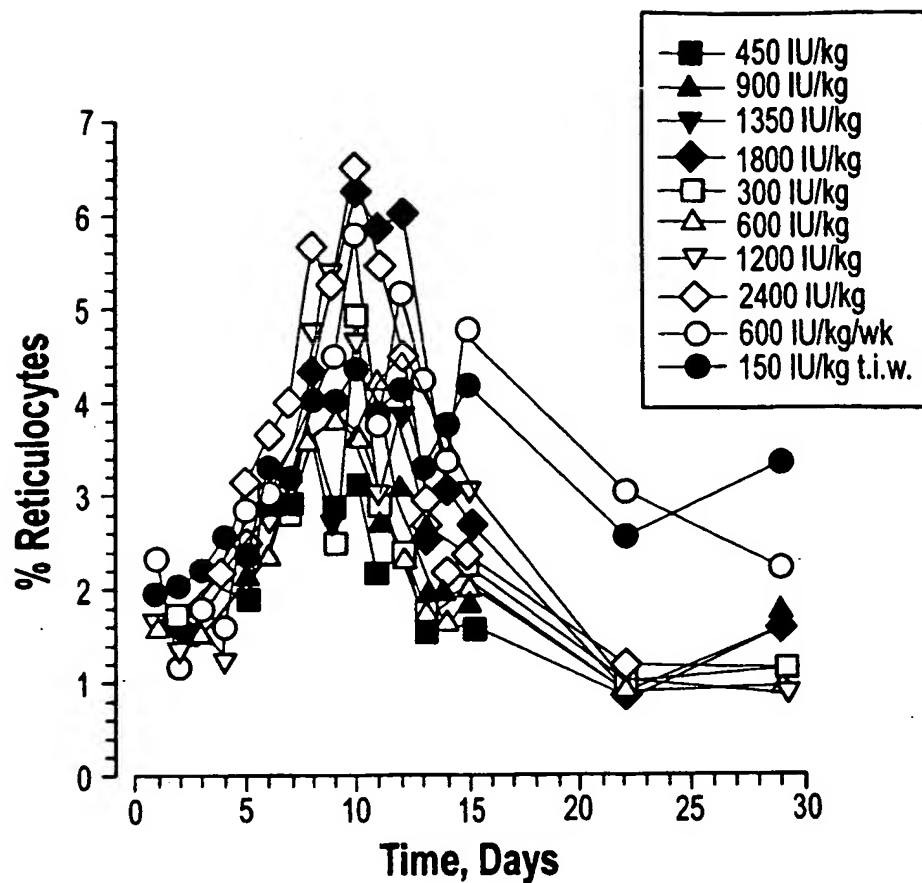


FIG. 27

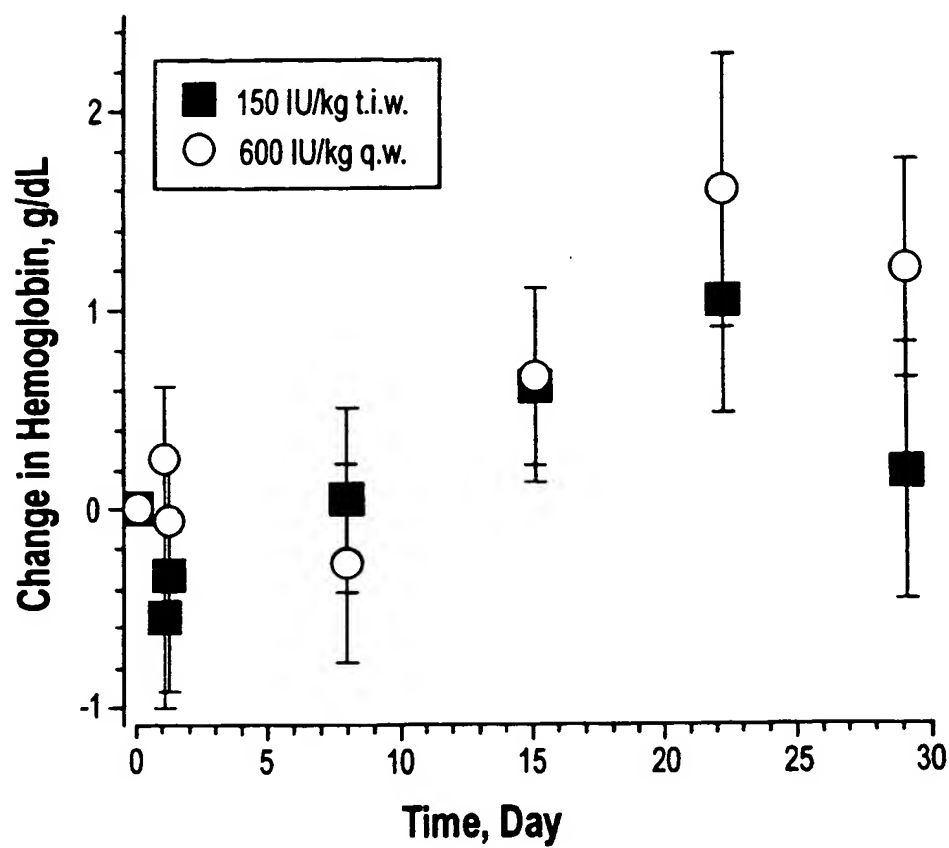


FIG. 28

### DEMOGRAPHIC DATA OF SUBJECTS IN CLINICAL STUDY EPO-PHI-370

TREATMENT	GENDER	WEIGHT (kg)	AGE (yr)	BASELINE HEMOGLOBIN (g/dL)
150 IU/kg t.i.w.	Male (N = 9)	74.3 ± 8.5 (63.2-85.0)	32.1 ± 5.5 (26.0-41.0)	14.7 ± 0.8 (13.5-15.6)
	Female (N = 15)	62.4 ± 10.3 (50.5-76.8)	34.6 ± 7.3 (21.0-46.0)	13.1 ± 0.9 (11.6-14.8)
	Overall (N = 24)	66.8 ± 11.1 (50.5-85.0)	33.7 ± 6.7 (21.0-46.0)	13.7 ± 1.1 (11.6-15.6)
	Male (N = 14)	72.4 ± 7.0 (61.8-84.5)	32.1 ± 8.6 (19.0-44.0)	14.6 ± 0.6 (13.5-15.6)
	Female (N = 8)	65.2 ± 7.8 (57.3-81.4)	35.1 ± 9.9 (19.0-45.0)	13.1 ± 0.7 (11.9-13.9)
40,000 IU q.w.	Overall (N = 22)	69.8 ± 8.0 (57.3-84.5)	33.2 ± 9.0 (19.0-45.0)	14.1 ± 1.0 (11.9-15.6)

FIG. 29

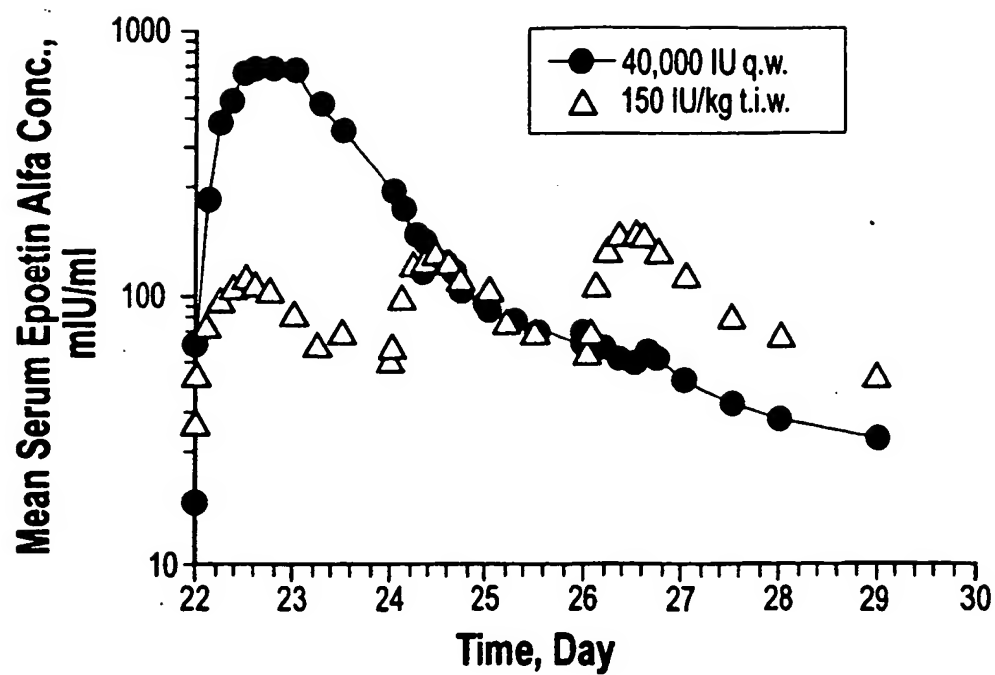


FIG. 30

# **MEAN $\pm$ SD (%CV) PHARMACOKINETIC PARAMETERS (PROTOCOL EPO-PHI-370)**

Parameter	150 (IU/kg t.i.w.)	40,000 (IU q.w.)	RATIO <sup>a</sup>
C <sub>max</sub> (mIU/mL)	191 $\pm$ 100 (52.3%)	785 $\pm$ 427 (54.4%)	4.11
C <sub>min</sub> (mIU/mL)	39 $\pm$ 18 (45.9%)	13 $\pm$ 9 (73.1%)	0.33
t <sub>max</sub> (h)	ND	18 $\pm$ 5 (29.4%)	ND
AUC(0-168) (mIU•h/mL)	13446 $\pm$ 4374 (32.5%)	30084 $\pm$ 13516 (44.9%)	2.24
CL/F (mL/h/kg)	37.1 $\pm$ 12.3 (33.1)	23.2 $\pm$ 10.8 (46.5)	0.63

<sup>a</sup> Parameter ratio of the mean values, 40,000 IU q.w./150 IU/kg t.i.w.  
ND = Not Determined

**FIG. 31**



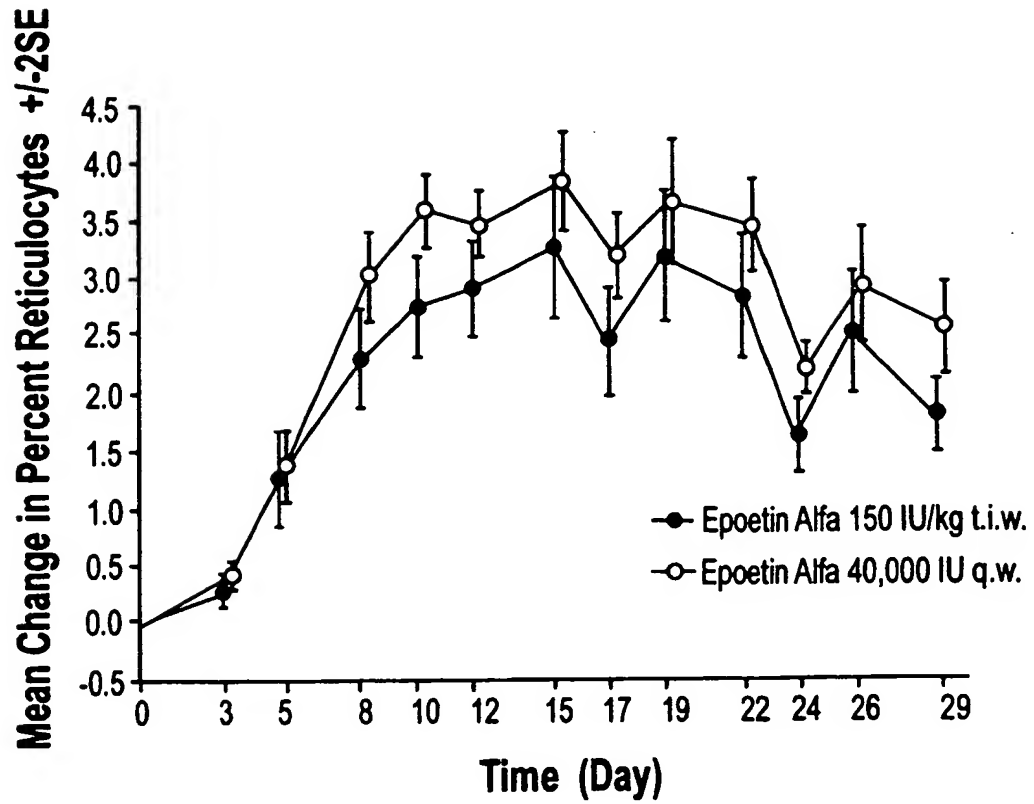


FIG. 32

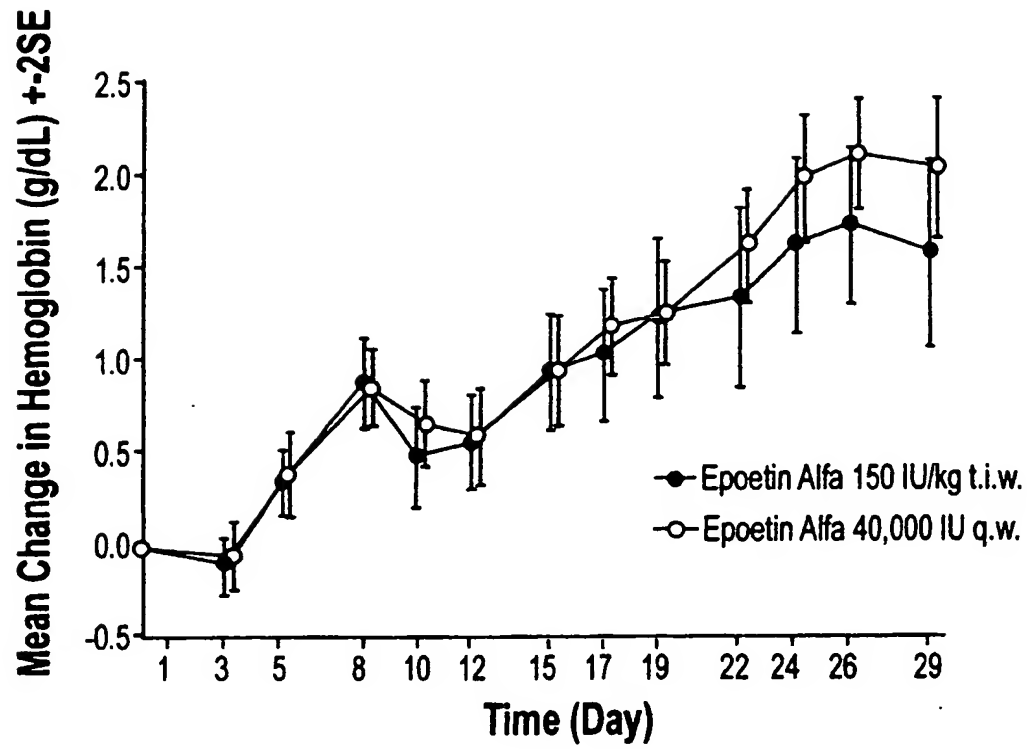


FIG. 33

**Mean  $\pm$  SD (%CV) Pharmacodynamic Parameters Corrected for Baseline Value (Protocol EPO-PHI-370)**

Treatment Group	Auc(RETI) <sup>a</sup> (%·d)	AUC(HEMO) <sup>b</sup> (g·d/dL)	AUC(RBC) <sup>c</sup> ( $\times 10^{12}$ cells·d/L)
150 IU/kg t.i.w.			
Male (N = 9)	56.8 $\pm$ 21.5 (37.8%)	26.4 $\pm$ 11.6 (43.7%)	12.0 $\pm$ 4.6 (37.8%)
Female (N = 15)	66.6 $\pm$ 19.8 (29.7%)	28.7 $\pm$ 18.6 (64.9%)	12.3 $\pm$ 5.5 (44.9%)
All Subjects (N = 24)	62.9 $\pm$ 20.5 <sup>d</sup> (32.7%)	27.9 $\pm$ 16.1 (57.8%)	12.2 $\pm$ 5.1 (41.7%)
40,000 IU q.w.			
Male (N = 14)	75.5 $\pm$ 9.8 (12.9%)	35.3 $\pm$ 11.2 (31.8%)	14.1 $\pm$ 4.0 (28.6%)
Female (N = 8)	80.3 $\pm$ 10.1 (12.5%)	23.5 $\pm$ 11.5 (48.8%)	10.9 $\pm$ 3.3 (30.6%)
All Subjects (N = 22)	77.2 $\pm$ 9.9 <sup>d</sup> (12.8%)	31.0 $\pm$ 12.5 (40.3%)	12.9 $\pm$ 4.0 (31.1%)
Ratio for All Subjects <sup>e</sup>	1.23	1.11	1.06
All Females <sup>f</sup> (N = 23)	71.3 $\pm$ 18.0 (25.3%)	26.9 $\pm$ 16.4 (61.0%)	11.8 $\pm$ 4.9 (41.0%)
All Males <sup>g</sup> (N = 23)	68.2 $\pm$ 17.7 (25.9%)	31.8 $\pm$ 12.0 (37.6%)	13.3 $\pm$ 4.3 (32.0%)

**FIG. 34**

### Mean $\pm$ SD Demographic Data of Subjects in Clinical Study EPO-PHI-373

Treatment	Gender	Weight (kg)	Age (yr)	Baseline Hemoglobin (g/dL)
150 IU/kg t.i.w.	Male (N = 9)	72.1 $\pm$ 8.2 (64.5-90.5)	26.4 $\pm$ 5.2 (21.0-37.0)	14.0 $\pm$ 0.4 (13.2-14.8)
	Female (N = 8)	61.0 $\pm$ 4.8 (53.3-66.4)	24.3 $\pm$ 3.5 (20.0-29.0)	12.8 $\pm$ 0.7 (11.7-13.8)
	Overall (N = 17)	66.9 $\pm$ 8.7 (53.3-90.5)	25.4 $\pm$ 4.5 (20.0-37.0)	13.4 $\pm$ 0.8 (11.7-14.8)
40,000 IU q.w.	Male (N = 9)	77.0 $\pm$ 12.8 (67.3-106)	29.4 $\pm$ 5.5 (19.0-36.0)	13.9 $\pm$ 0.5 (13.3-14.6)
	Female (N = 8)	63.7 $\pm$ 8.8 (51.0-78.0)	26.5 $\pm$ 7.5 (18.0-41.0)	13.0 $\pm$ 0.8 (12.2-14.2)
	Overall (N = 17)	70.7 $\pm$ 12.7 (51.0-106)	28.1 $\pm$ 6.5 (18.0-41.0)	13.5 $\pm$ 0.8 (12.2-14.6)

FIG. 35

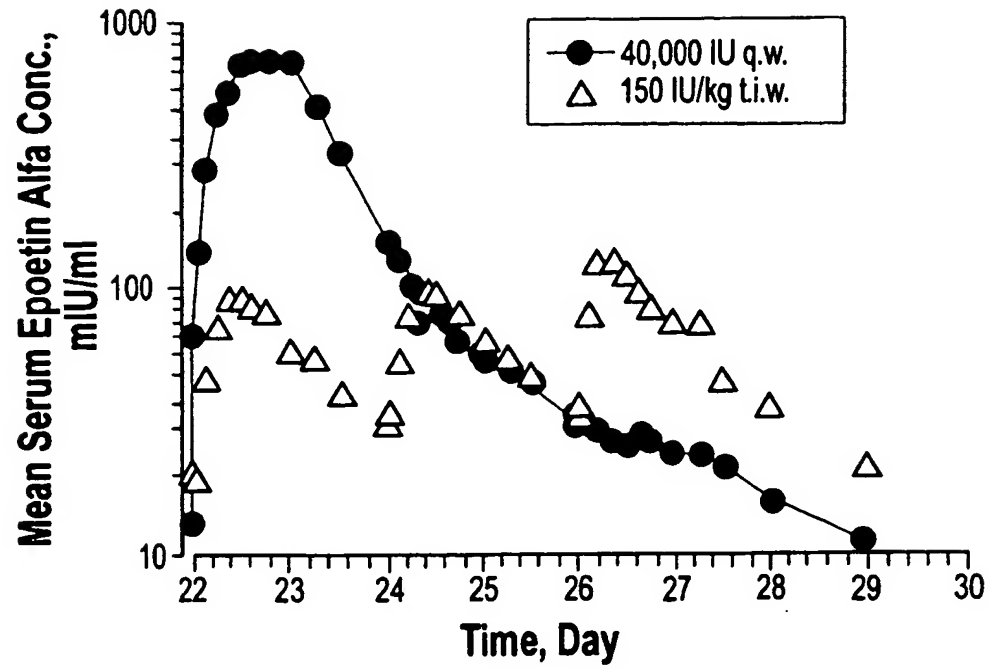


FIG. 36

### Mean $\pm$ SD Pharmacokinetic Parameters (Protocol EPO-PHI-373)

Parameter	150 (IU/kg t.i.w.)	40,000 (IU q.w.)	Ratio <sup>a</sup>
C <sub>max</sub> (mIU/mL)	143 $\pm$ 54 (37.8%)	861 $\pm$ 445 (51.7%)	6.02(13.2-14.8)
C <sub>min</sub> (mIU/mL)	18 $\pm$ 9 (50.7%)	3.8 $\pm$ 4.3 (114%)	0.21
t <sub>max</sub> (h)	ND	16 $\pm$ 8 (45.6%)	ND
AUC(0-168) (mIU·h/mL)	8587 $\pm$ 1521 (17.7%)	25747 $\pm$ 9062 (35.2%)	3.00
CL/F (mL/h/kg)	51.4 $\pm$ 10.1 (18.7%)	24.7 $\pm$ 7.2 (29.1%)	0.46

<sup>a</sup> Parameter ratio of the mean values, 40,000 IU q.w./150 IU/kg t.i.w.

ND = not determined

**FIG. 37**

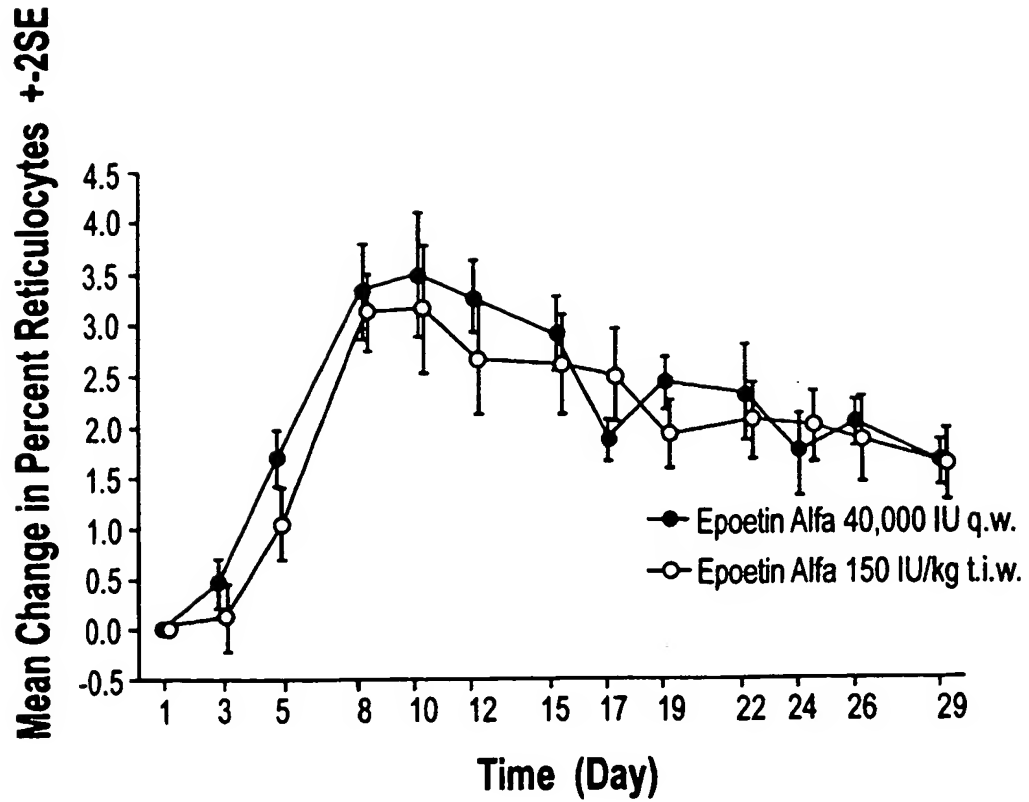


FIG. 38

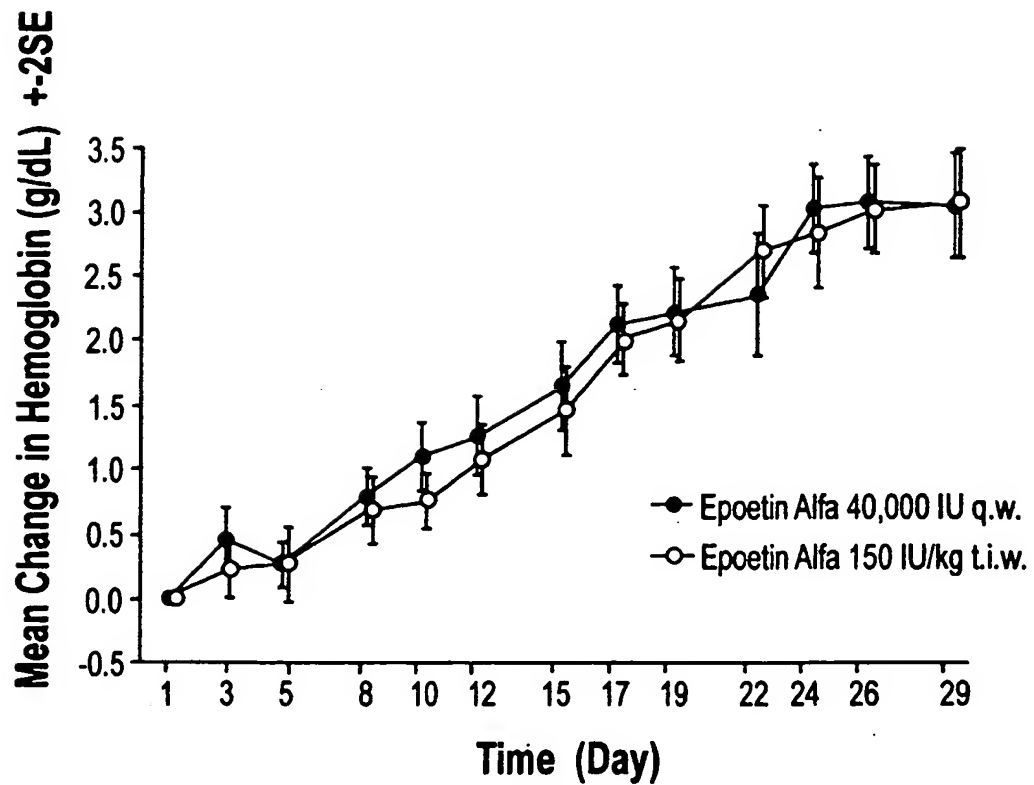


FIG. 39



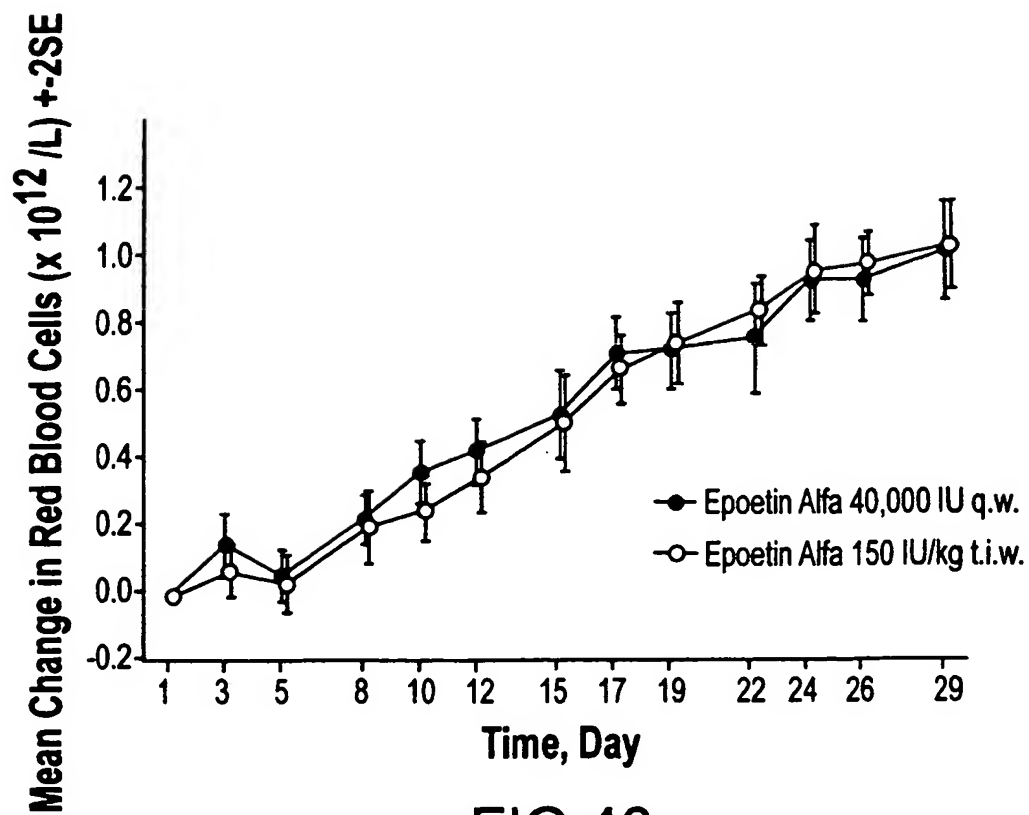


FIG.40

**Mean  $\pm$  SD (%CV) Pharmacodynamic Parameters Corrected for Baseline Value (Protocol EPO-PHI-373)**

Treatment Group	Auc(RETI) <sup>a</sup> (%·d)	AUC(HEMO) <sup>b</sup> (g·d/dL)	AUC(RBC) <sup>c</sup> ( $\times 10^{12}$ ·d/L)
150 IU/kg t.i.w.			
Male (N = 9)	55.1 $\pm$ 14.4 (23.1%)	40.4 $\pm$ 13.0 (32.3%)	13.4 $\pm$ 3.9 (29.3%)
Female (N = 8)	59.6 $\pm$ 21.3 (35.7%)	51.1 $\pm$ 10.9 (21.4%)	16.4 $\pm$ 4.4 (26.7%)
All Subjects (N = 17)	57.2 $\pm$ 17.5 (30.6%)	45.4 $\pm$ 12.9 (28.5%)	14.8 $\pm$ 4.3 (29.0%)
40,000 IU q.w.			
Male (N = 9)	58.8 $\pm$ 10.4 (17.7%)	43.5 $\pm$ 11.6 (26.6%)	13.6 $\pm$ 4.3 (31.3%)
Female (N = 8)	68.4 $\pm$ 14.4 (21.1%)	52.4 $\pm$ 15.0 (28.6%)	16.9 $\pm$ 4.3 (25.5%)
All Subjects (N = 17)	63.3 $\pm$ 13.0 (20.5%)	47.7 $\pm$ 13.6 (28.6%)	15.1 $\pm$ 4.5 (29.5%)
Ratio for All Subjects <sup>d</sup>	1.11	1.05	1.02
All Females <sup>e</sup> (N = 16)	64.0 $\pm$ 18.1 (28.3%)	51.7 $\pm$ 12.7g (24.5%)	16.6 $\pm$ 4.2g (25.3%)
All Males <sup>f</sup> (N = 18)	57.0 $\pm$ 12.3 (21.6%)	41.9 $\pm$ 12.0g (28.7%)	13.5 $\pm$ 4.0g (29.5%)

**FIG. 41**

Mean = SD (%CV) Pharmacokinetic Parameters (Clinical Studies EPO-PHI-358, EPO-PHI-359, EPO-PHI-370, and EPO-PHI-373)						
Study	Dose	C <sub>max</sub> (mIU/mL)	t <sub>max</sub> (h)	AUC <sup>a</sup> (mIU·h/mL)	CL/F (mL/h/kg)	t <sub>1/2</sub> (h)
Single Subcutaneous Dose Administration						
EPO359	300 IU/kg	429 ± 86 (20.0%)	22.8 ± 8.1 (36.5%)	20056 ± 4138 (20.6%)	15.5 ± 3.1 (20.2%)	68.2 ± 52.2 (76.6%)
EPO358	450 IU/kg	1263 ± 290 (23.0%)	15.6 ± 5.8 (37.0%)	45498 ± 12342 (27.1%)	10.4 ± 2.6 (24.9%)	24.2 ± 3.2 (13.2%)
EPO359	600 IU/kg	1263 ± 486 (38.5%)	27.6 ± 9.1 (33.0%)	55475 ± 16384 (29.5%)	11.8 ± 4.2 (35.5%)	29.3 ± 9.4 (32.0%)
EPO358	900 IU/kg	2235 ± 599 (26.8%)	22.2 ± 12.7 (57.0%)	103154 ± 28024 (27.2%)	9.36 ± 2.97 (31.7%)	36.0 ± 13.5 (37.3%)
EPO359	1200 IU/kg	2256 ± 710 (31.4%)	26.4 ± 7.8 (29.4%)	119932 ± 44217 (36.9%)	11.2 ± 4.2 (37.7%)	78.5 ± 95.4 (122%)
EPO358	1350 IU/kg	3755 ± 879 (23.4%)	23.4 ± 8.8 (37.8%)	174193 ± 41417 (23.8%)	8.23 ± 2.57 (31.3%)	33.4 ± 2.4 (7.2%)
EPO358	1800 IU/kg	4370 ± 1673 (38.3%)	28.8 ± 7.8 (27.2%)	258600 ± 101175 (39.1%)	7.64 ± 2.22 (29.1%)	32.4 ± 8.4 (25.9%)
EPO359	2400 IU/kg	6819 ± 764 (11.2%)	25.2 ± 6.2 (24.7%)	429441 ± 32139 (7.5%)	5.61 ± 0.44 (7.8%)	43.6 ± 25.9 (59.5%)
Multiple Subcutaneous Dose Administration						
EPO358	150 IU/kg	252 ± 71 (28.0%)	NA	16582 ± 4256 (25.7%)	28.7 ± 7.8 (27.1%)	25.9 ± 7.1 (27.2%)
Wk 4	t.i.w.					
EPO359	600 IU/kg	1502 ± 384 (25.6%)	21.6 ± 6.1 (28.5%)	63439 ± 10893 (17.2%)	9.70 ± 1.8 (18.1%)	28.3 ± 7.5 (26.3%)
Wk 1	q.w.					
EPO359	600 IU/kg	1278 ± 213 (16.6%)	24.0 ± 8.7 (36.4%)	50725 ± 6774 (13.4%)	12.0 ± 1.6 (13.2%)	28.1 ± 7.0 (24.9%)
Wk 4	q.w.					

FIG. 42

$\frac{1}{2}$

Applicant: The R.W. Johnson Pharmaceutical Research Institute						
Drug: Epoetin Alfa Once Weekly Dosing						
NDA No.: Insert NDA No.						
Study	Dose	C <sub>max</sub> (mIU/mL)	t <sub>max</sub> (h)	AUC <sup>a</sup> (mIU·h/mL)	CL/F (mL/h/kg)	t <sub>1/2</sub> (h)
Single Subcutaneous Dose Administration						
EPO370 Wk 4	150 IU/kg t.i.w.	191 ± 100 (52.3%)	NA	13446 ± 4374 (32.5%)	37.1 ± 12.3 (33.1%)	31.8 ± 13.4 (42.1%)
EPO370 Wk 4	40,000 IU q.w.	785 ± 427 (54.4% <sup>0</sup> )	18 ± 5 (29.4%)	30084 ± 13516 (44.9%)	23.2 ± 10.8 (46.5%)	39.3 ± 7.1 (18.1%)
EPO373 Wk 4	150 IU/kg t.i.w.	143 ± 54 (37.8%)	NA	8587 ± 1521 (17.7%)	54.1 ± 10.1 (18.7%)	19.4 ± 8.1 (41.5%)
EPO373 Wk 4	40,000 IU q.w.	861 ± 445 (51.7%)	16 ± 8 (45.6%)	25,747 ± 9062 (35.2%)	24.7 ± 7.2 (29.1%)	15.0 ± 6.1 (40.9%)

<sup>a</sup> AUC(0-168) during a dose week for multiple dose regimens and AUC(0-672) during the 4-wk of study period for single doses.

NA = Not applicable

FIG. 42

$\frac{1}{2}$

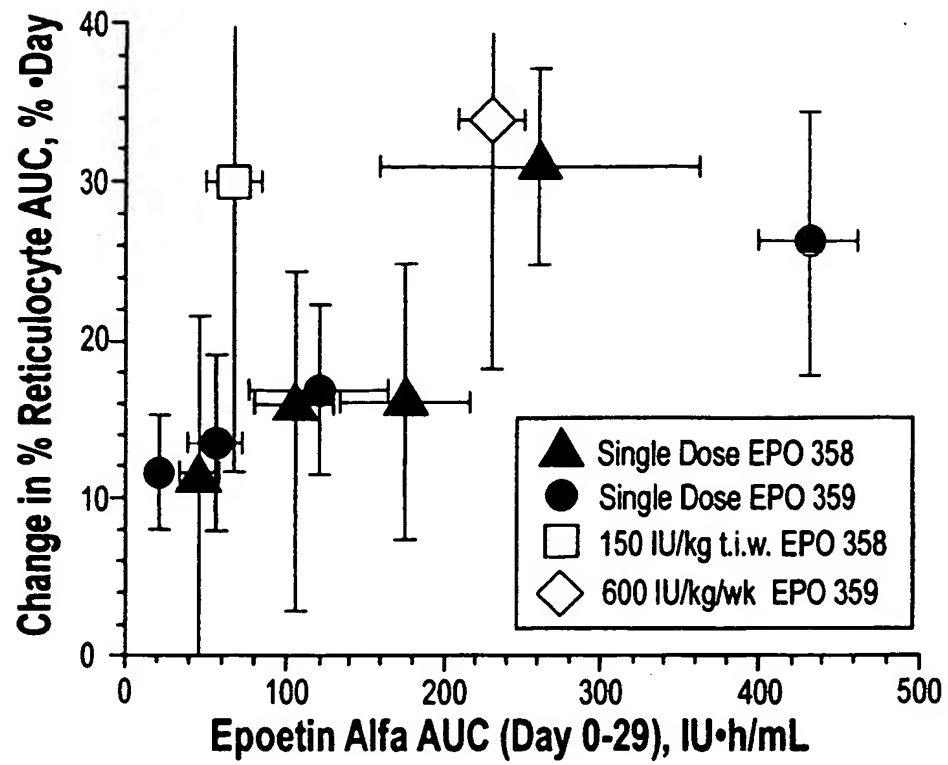


FIG. 43

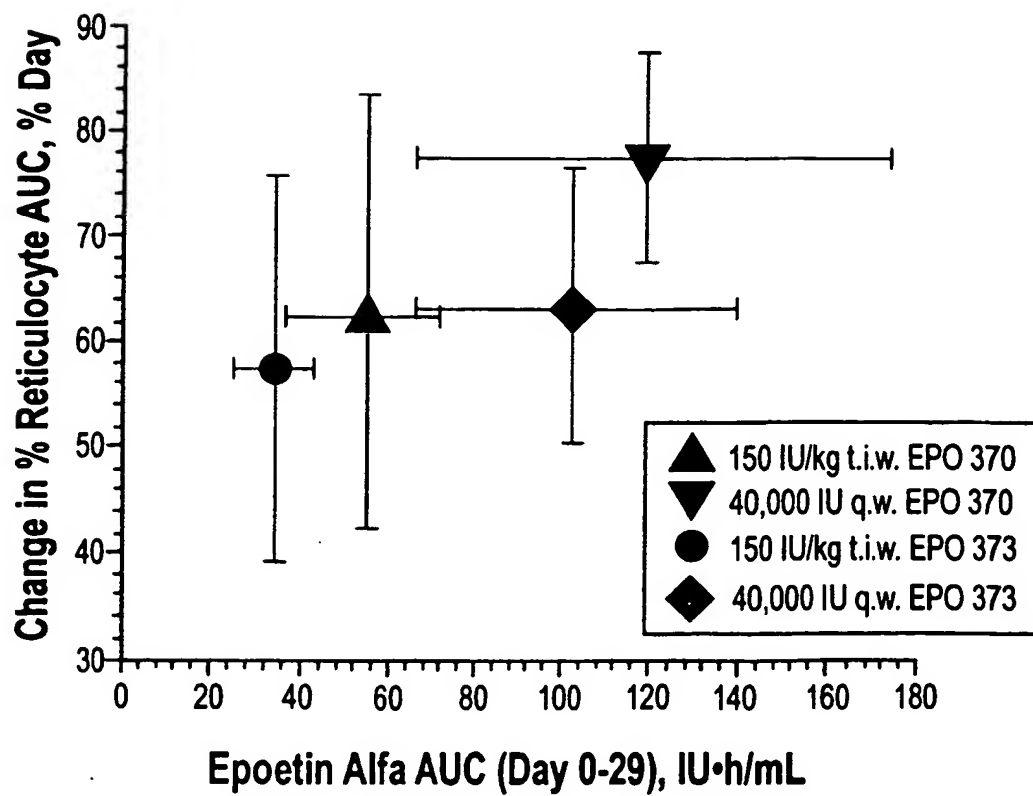


FIG. 44

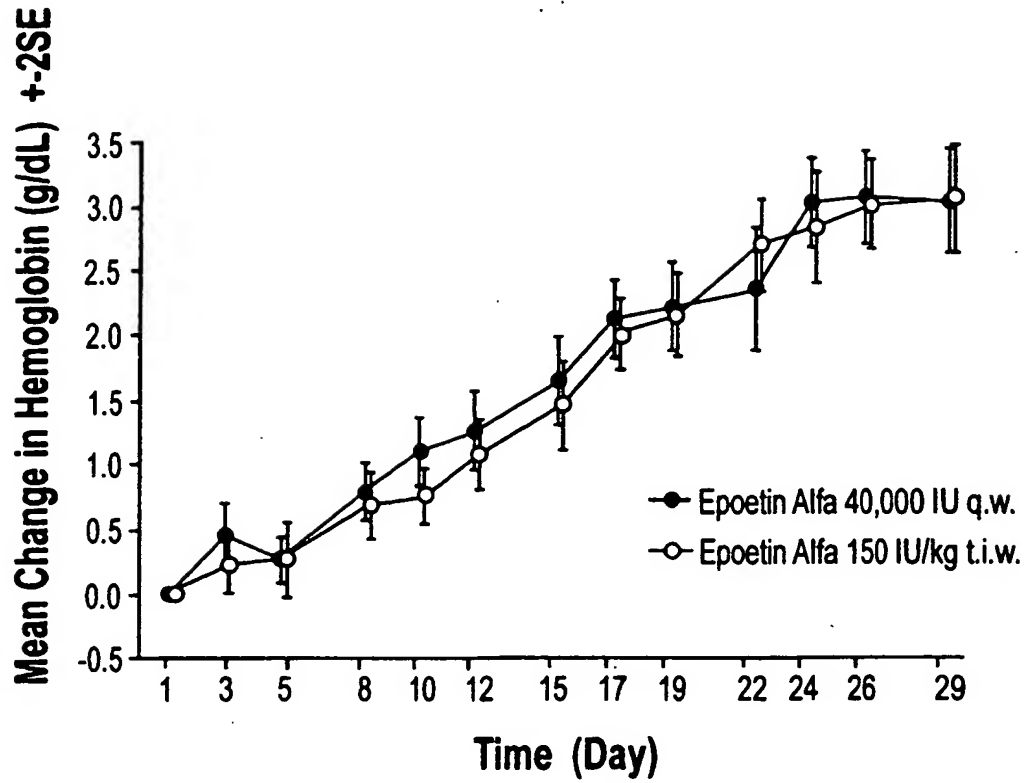


FIG. 45

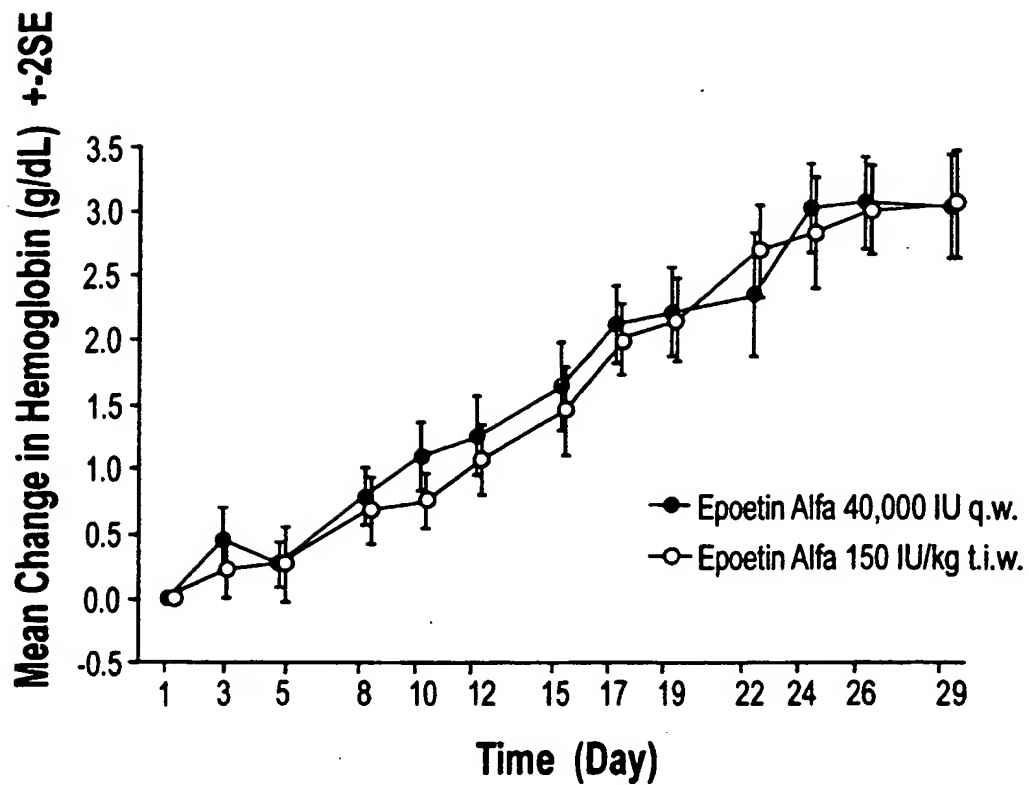


FIG. 46



### Demographic and Baseline Characteristics (All Subjects in Protocol EPO-PHI-373)

Characteristic	Epoetin Alfa 150 IU/kg t.i.w. (N=18)	Epoetin Alfa 40,000 IU q.w. (N=18)	Total (N=36)
<b>Sex</b>			
Male	9 (50%)	9 (50%)	18 (50%)
Female	9 (50%)	9 (50%)	18 (50%)
<b>Age (years)</b>			
Mean (SD)	25.3 (4.34)	27.7 (6.48)	26.5 (5.57)
Median	24	27.5	25.0
Range	20.0-37.0	18.0-41.0	18.0-41.0
<b>Weight (kg)</b>			
Mean (SD)	66.8 (8.47)	70.3 (12.51)	68.6 (10.67)
Median	66.0	69.0	67.3
Range	53.3-90.5	51.0-105.5	51.0-105.5
<b>Height (cm)</b>			
Mean (SD)	171.9 (6.94)	170.9 (8.86)	171.4 (7.86)
Median	172.8	169.5	171.8
Range	160.5-191.0	160.5-191.0	160.5-191.0
<b>Race</b>			
White	17 (94%)	15 (83%)	32 (89%)
Black	1 (6%)	2 (11%)	3 (8%)
Other	0 (0%)	1 (6%)	1 (3%)

FIG. 47

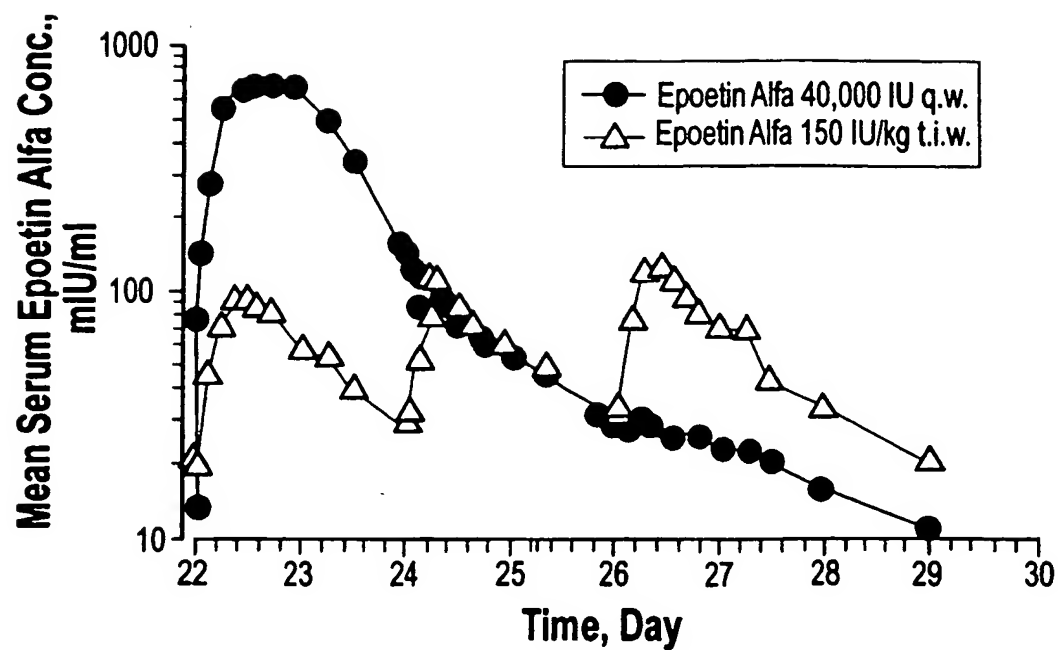


FIG. 48

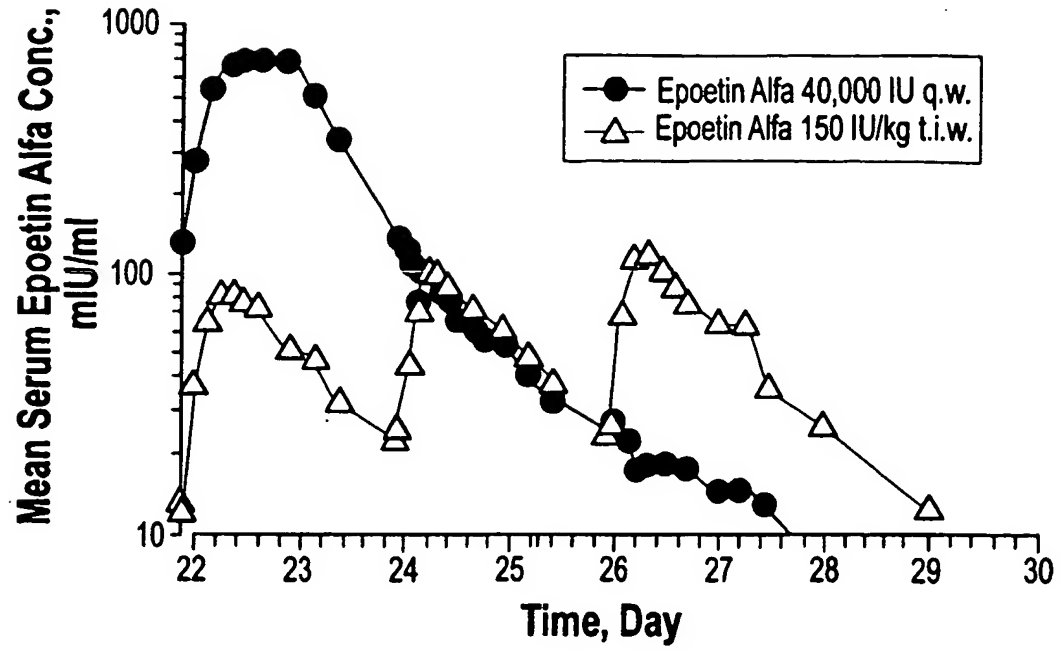


FIG. 49

**SELECTED MEAN (SD) [%CV] PHARMACOKINETIC PARAMETERS  
(SUBJECTS IN THE EFFICACY POPULATION IN PROTOCOL EPO-PHI-373)**

Parameter	150 IU/kg t.i.w. (n=17)		40,000 IU q.w. (n=17)		Ratio <sup>a</sup>
	Mean (SD)	[%CV]	Mean (SD)	[%CV]	
C <sub>max</sub> (mIU/mL)	143 (54)	[37.8%]	861 (445)	[51.7%]	6.02
C <sub>min</sub> (mIU/mL)	18 (9)	[50.7%]	3.8 (4.3)	[114%]	0.21
t <sub>max</sub> (h)	ND		16 (8)	[45.6%]	ND
AUC <sub>(0-168)</sub> (mIU•h/mL)	8587 (1521)	[17.7%]	25747 (9062)	[35.2%]	3.00
CL/F (mL/h/kg)	54.1 (10.1)	[18.7%]	24.7 (7.2)	[29.1%]	0.46

<sup>a</sup> Parameter ratio of the mean values, 40,000 IU q.w./150 IU/kg t.i.w.  
ND = Not determined

**FIG. 50**

**MEAN (SD) CHANGE FROM BASELINE IN PERCENT  
RETICULOCYTES (SUBJECTS IN THE EFFICACY  
POPULATION-PROTOCOL EPO-PHI-373)**

	Epoetin Alfa 150 IU/kg t.i.w.			Epoetin Alfa 40,000 IU/kg q.w.		
	N	Mean (SD)	Range	N	Mean (SD)	Range
<b>Baseline</b>	17	1.5 (0.59)	0.9-2.9	17	1.4 (0.45)	0.8-2.5
<b>Change from Baseline to Day</b>						
Day 3	17	1.1 (0.68)	-2.0-1.3	17	0.5 (0.51)	-0.3-1.8
Day 5	17	1.1 (0.76)	-1.0-2.2	17	1.7 (0.56)	0.5-2.7
Day 8	17	3.1 (0.77)	1.9-4.3	17	3.3 (0.97)	2.0-5.3
Day 10	17	3.2 (1.30)	1.8-5.5	17	3.5 (1.26)	1.4-6.8
Day 12	17	2.7 (1.12)	0.3-5.4	17	3.3 (0.74)	2.0-5.5
Day 15	17	2.6 (1.02)	1.0-4.8	17	2.9 (0.76)	1.6-4.9
Day 17	17	2.5 (0.94)	-1.7-5.4	17	1.9 (0.42)	1.3-2.7
Day 19	17	1.9 (0.74)	-0.0-3.4	17	2.4 (0.53)	1.7-3.6
Day 22	17	2.1 (0.78)	-0.1-2.9	17	2.4 (1.00)	0.7-4.5
Day 24	17	2.0 (0.73)	0.3-3.1	16	1.7 (0.82)	-0.0-3.2
Day 26	17	1.9 (0.90)	-0.3-4.0	17	2.1 (0.47)	1.0-2.7
Day 29	17	1.7 (0.74)	-0.3-3.2	17	1.7 (0.46)	1.0-2.7
Last Visit	17	1.7 (0.74)	-0.3-3.2	17	1.7 (0.46)	1.0-2.7

**FIG. 51**

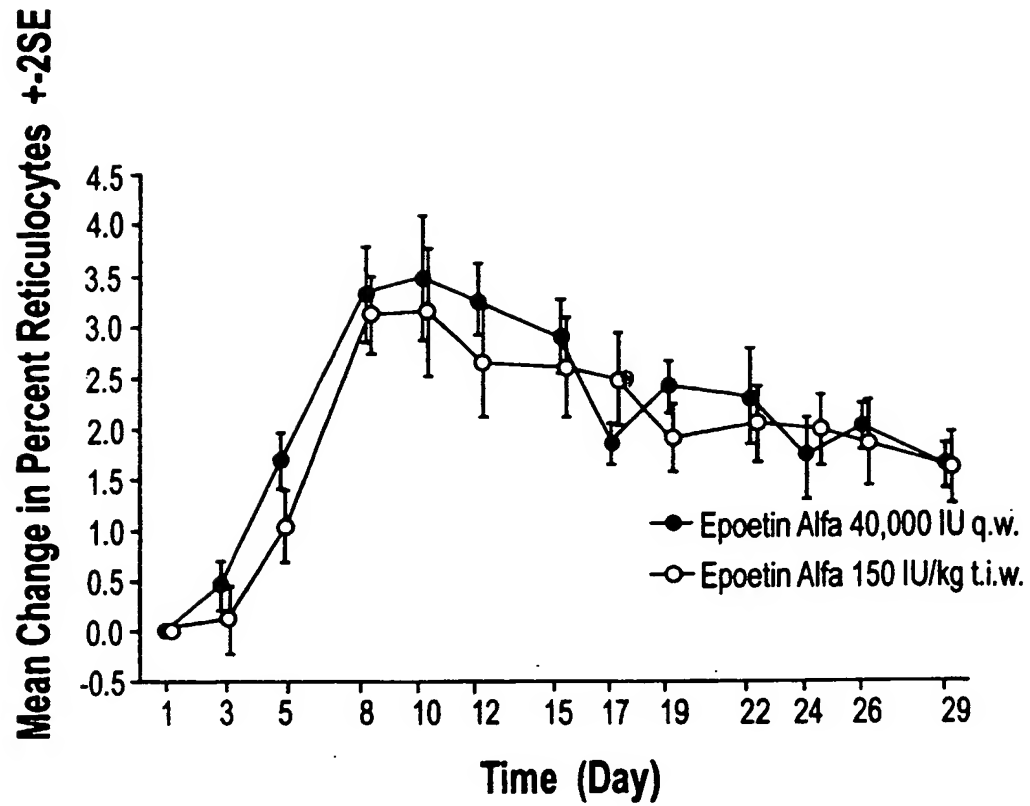


FIG. 52

**MEAN (SD) CHANGE FROM BASELINE IN HEMOGLOBIN (g/dL)  
(SUBJECTS IN THE EFFICACY POPULATION-PROTOCOL EPO-PHI-373)**

	<u>Epoetin Alfa 150 IU/kg t.i.w.</u>			<u>Epoetin Alfa 40,000 IU/kg q.w.</u>		
	N	Mean (SD)	Range	N	Mean (SD)	Range
<b>Baseline</b>	17	13.4 (0.81)	11.7-14.8	17	13.5 (0.79)	12.2-14.6
<b>Change from Baseline to Day</b>						
Day 3	17	0.2 (0.45)	-0.5-1.1	17	0.5 (0.52)	-0.5-1.5
Day 5	17	1.3 (0.63)	-0.6-1.8	17	0.3 (0.37)	-0.4-0.8
Day 8	17	0.7 (0.54)	-0.4-1.8	17	0.8 (0.47)	1.0-1.7
Day 10	17	0.8 (0.45)	-0.2-1.5	17	1.1 (0.56)	0.2-2.4
Day 12	17	1.1 (0.57)	0.4-2.2	17	1.3 (0.65)	0.1-2.4
Day 15	17	1.5 (0.72)	0.2-2.4	17	1.7 (0.73)	0.2-2.7
Day 17	17	2.0 (0.57)	1.0-3.0	17	2.1 (0.62)	1.0-3.2
Day 19	17	2.2 (0.68)	1.2-3.2	17	2.2 (0.69)	1.2-3.2
Day 22	17	2.7 (0.74)	1.4-3.9	17	2.4 (1.00)	0.7-4.7
Day 24	17	2.9 (0.90)	0.7-4.2	16	3.0 (0.70)	1.6-4.0
Day 26	17	3.0 (0.69)	1.8-4.3	17	3.1 (0.74)	1.9-4.4
Day 29	17	3.1 (0.86)	1.4-4.5	17	3.1 (0.84)	1.8-4.6
Last Visit	17	3.1 (0.86)	1.4-4.5	17	3.1 (0.84)	1.8-4.6

**FIG. 53**

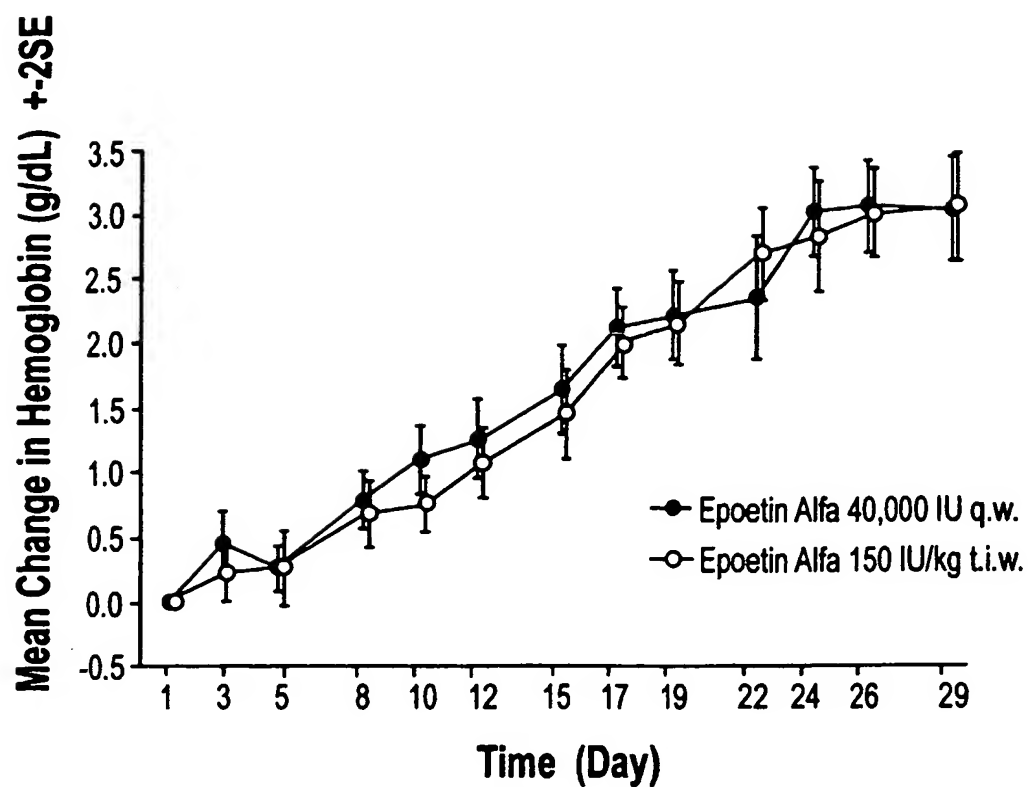


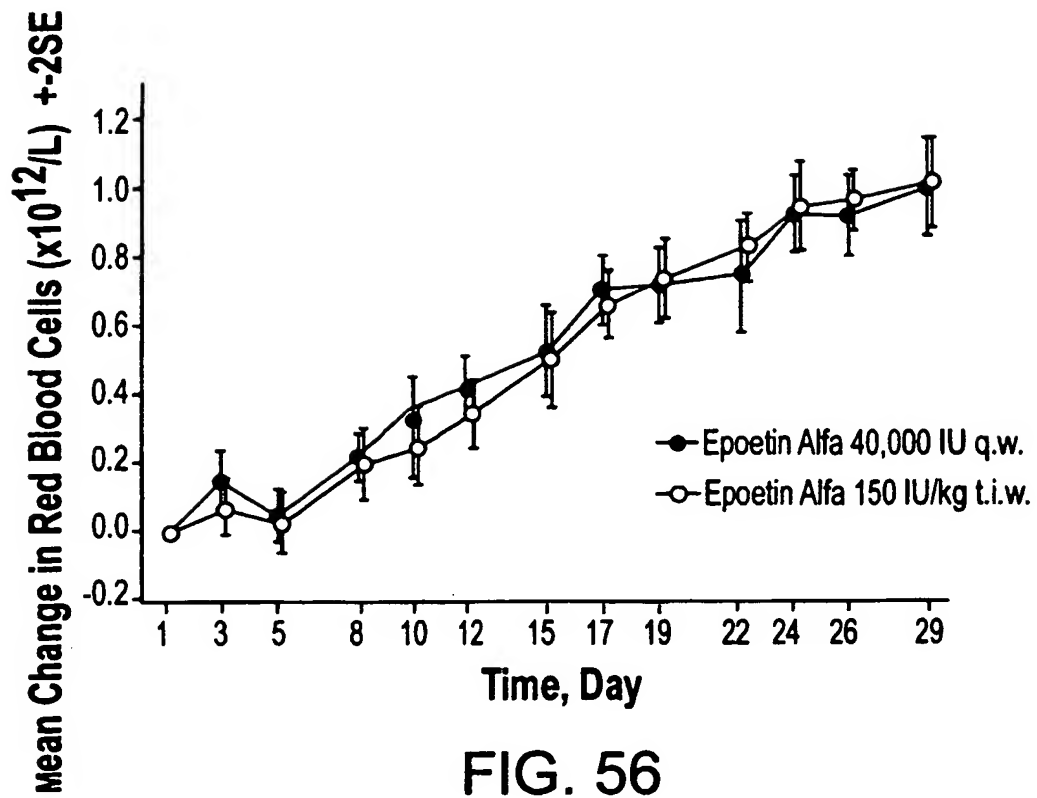
FIG. 54



**MEAN (SD) CHANGE FROM BASELINE IN RED BLOOD CELLS ( $\times 10^{12}/L$ )  
(SUBJECTS IN THE EFFICACY POPULATION-PROTOCOL EPO-PHI-373)**

	Epoetin Alfa 150 IU/kg t.i.w.			Epoetin Alfa 40,000 IU/kg q.w.		
	N	Mean (SD)	Range	N	Mean (SD)	Range
<b>Baseline</b>	17	4.4 (0.30)	3.8-5.1	17	4.4 (0.26)	4.0-4.8
<b>Change from Baseline to Day</b>						
Day 3	17	0.1 (0.16)	-0.2-0.4	17	0.2 (0.19)	-0.2-0.5
Day 5	17	0.0 (0.18)	-0.2-0.4	17	0.1 (0.15)	-0.2-0.3
Day 8	17	0.2 (0.21)	-0.2-0.8	17	0.2 (0.14)	0.0-0.5
Day 10	17	0.2 (0.17)	-0.1-0.5	17	0.4 (0.18)	0.1-0.8
Day 12	17	0.3 (0.21)	-0.1-0.7	17	0.4 (0.20)	-0.0-0.7
Day 15	17	0.5 (0.29)	0.0-0.9	17	0.5 (0.27)	-0.1-0.9
Day 17	17	0.7 (0.20)	0.3-1.0	17	0.7 (0.21)	0.4-1.1
Day 19	17	0.7 (0.24)	0.3-1.1	17	0.7 (0.22)	0.3-1.1
Day 22	17	0.8 (0.20)	0.5-1.2	17	0.8 (0.34)	0.2-1.4
Day 24	17	1.0 (0.28)	0.3-1.3	16	0.9 (0.23)	0.4-1.2
Day 26	17	1.0 (0.18)	0.7-1.3	17	0.9 (0.25)	0.4-1.3
Day 29	17	1.0 (0.27)	0.5-1.4	17	1.0 (0.30)	0.4-1.4
Last Visit	17	1.0 (0.27)	0.5-1.4	17	1.0 (0.30)	0.4-1.4

**FIG. 55**



**MEAN (SD) [%CV] PHARMACODYNAMIC PARAMETERS CORRECTED  
FOR BASELINE VALUE  
(EFFICACY POPULATION IN PROTOCOL EPO-PHI-373)**

TREATMENT GROUP	AUC(RETI) <sup>a</sup> (%.d)		AUC(HEMO) <sup>b</sup> (g.d/dL)		AUC(RBC) <sup>c</sup> (x10 <sup>12</sup> .d/L)	
	MEAN (SD)	[%CV]	MEAN (SD)	[%CV]	MEAN (SD)	[%CV]
<b>150 IU/kg t.i.w.</b>						
Male (N=9)	55.1 (14.4)	[26.1%]	40.4 (13.0)	[32.2%]	13.4 (3.9)	[29.3%]
Female (N=8)	59.6 (21.3)	[35.7%]	51.1 (10.9)	[21.4%]	16.4 (4.4)	[26.7%]
All Subjects (N=17)	57.2 (17.5)	[30.6%]	45.4 (12.9)	[28.5%]	14.8 (4.3)	[29.0%]
<b>40,000 IU q.w.</b>						
Male (N=9)	58.8 (10.4)	[17.7%]	43.5 (1	1.6)	13.6 (4.3)	[31.3%]
Female (N=8)	68.4 (14.4)	[21.1%]	52.4 (15.0)	[28.6%]	16.9 (4.3)	[25.5%]
All Subjects (N=17)	63.3 (13.0)	[20.5%]	47.7 (13.6)	[28.6%]	15.1 (4.5)	[29.5%]
Ratio for All Subjects <sup>d</sup>	1.1	1	1.05		1.02	
All Females <sup>e</sup> (N=16)	64.0 (18.1)	[28.3%]	51.7 (12.7)	<sup>g</sup> [24.5%]	16.6 (4.2)	<sup>g</sup> [25.3%]
All Males <sup>f</sup> (N=18)	57.0 (12.3)	[21.6%]	41.9 (12.0)	<sup>g</sup> [28.7%]	13.5 (4.0)	<sup>g</sup> [29.5%]

%CV = percent coefficient of variation

<sup>a</sup> AUC of % reticulocytes over the one month study period and corrected for predose baseline value.

<sup>b</sup> AUC of hemoglobin over the one month study period and corrected for predose baseline value.

<sup>c</sup> AUC of red blood cells over the one month study period and corrected for predose baseline value.

<sup>d</sup> Ratios of 40,000 IU q.w. to 150 IU/kg t.i.w. mean parameter values for all subjects.

<sup>e</sup> Including all female subjects in both treatment groups.

<sup>f</sup> Including all male subjects in both treatment groups.

<sup>g</sup> Statistically different (p<0.05) between male and female subjects

**FIG. 57**

Body System Preferred Term	Epoetin Alfa 150 IU/kg t.i.w. (N=18)	Epoetin Alfa 40,000 IU q.w. (N=18)
Any adverse event	13 (72%)	12 (67%)
Body as a whole - general disorders	6 (33%)	7 (39%)
Pain	4 (22%)	5 (28%)
Fatigue	2 (11%)	1 (6%)
Enlarged abdomen	1 (6%)	0 (0%)
Allergic reaction	0 (0%)	1 (6%)
Back pain	0 (0%)	1 (6%)
Center & periph nerv syst disorders	6 (33%)	6 (33%)
Headache	5 (28%)	5 (28%)
Dizziness	1 (6%)	2 (11%)
Hyperesthesia	1 (6%)	0 (0%)
Hypertonia	1 (6%)	0 (0%)
Skin and appendage disorders	6 (33%)	3 (17%)
Erythematous rash	5 (28%)	2 (11%)
Rash	2 (11%)	1 (6%)
Skin disorder	0 (0%)	1 (6%)
Localized skin reaction	1 (6%)	0 (0%)
Gastro-intestinal system disorders	4 (22%)	2 (11%)
Abdominal pain	2 (11%)	0 (0%)
Nausea	2 (11%)	0 (0%)
Constipation	1 (6%)	0 (0%)
Diarrhea	1 (6%)	0 (0%)
Gastroenteritis	0 (0%)	1 (6%)
Gingivitis	0 (0%)	1 (6%)
Toothache	1 (6%)	0 (0%)
Application site disorders	5 (28%)	1 (6%)
Injection site bruising	3 (17%)	1 (6%)
Application site reaction	2 (11%)	0 (0%)
Injection site pain	1 (6%)	0 (0%)
Respiratory system disorders	2 (11%)	1 (6%)
Upper respiratory tract infection	2 (11%)	0 (0%)
Pharyngitis	0 (0%)	1 (6%)
Rhinitis	0 (0%)	1 (6%)
Metabolic nutritional disorders	1 (6%)	1 (6%)
Thirst	1 (6%)	0 (0%)
Xerophthalmia	0 (0%)	1 (6%)
Musculo-skeletal system disorders	2 (11%)	0 (0%)
Myalgia	1 (6%)	0 (0%)
Skeletal pain	1 (6%)	0 (0%)
Psychiatric disorders	0 (0%)	2 (11%)
Insomnia	0 (0%)	1 (6%)
Somnolence	0 (0%)	1 (6%)

FIG. 58

1/  
2

Body System Preferred Term	Epoetin Alfa 150 IU/kg t.i.w. (N=18)	Epoetin Afa 40,000 IU q.w. (N=18)
Heart rate and rhythm disorders	0 (0%)	1 (6%)
Palpitation	0 (0%)	1 (6%)
Female reproductive disorders	1 (11%)*	0 (0%)
Dysmenorrhea	1 (11%)*	0 (0%)
Other special senses disorders	1 (6%)	0 (0%)
Taste perversion	1 (6%)	0 (0%)
Vascular (extracardiac) disorders	1 (6%)	0 (0%)
Phlebitis	1 (6%)	0 (0%)
Vision disorders	1 (6%)	0 (0%)
Conjunctivitis	1 (6%)	0 (0%)

\* Percentages taken as a percentage of the

$\frac{2}{2}$

FIG. 58

**Mean (SD) Change from Baseline in Iron Profile  
(All Subjects in Protocol EPO-PHI-373)**

	Epoetin Alfa 150 IU/kg t.i.w.			Epoetin Alfa 40,000 IU q.w.		
	N	Mean	(SD)	N	Mean	(SD)
<b>Serum Iron (<math>\mu\text{g/dL}</math>)</b>						
Baseline	18	97.1	(40.54)	18	102.7	(27.23)
Change from Baseline to Day 8	18	7.1	(79.56)	18	28.8	(95.05)
Change from Baseline to Day 15	18	34.7	(122.43)	17	49.6	(106.89)
Change from Baseline to Day 22	18	21.4	(108.34)	17	23.6	(95.73)
Change from Baseline to Day 29	17	-44.3	(43.76)	18	22.0	(78.18)
Change from Baseline to Last Visit	18	-33.5	(62.59)	18	22.0	(78.18)
<b>Ferritin (ng/mL)</b>						
Baseline	18	69.6	(25.17)	18	78.2	(31.36)
Change from Baseline to Day 8	18	-38.9	(13.13)	18	-37.9	(23.12)
Change from Baseline to Day 15	18	-37.6	(16.17)	17	-37.1	(31.52)
Change from Baseline to Day 22	18	-36.3	(22.79)	17	-43.0	(30.51)
Change from Baseline to Day 29	17	-41.5	(19.75)	18	-36.6	(37.18)
Change from Baseline to Last Visit	18	-38.1	(24.05)	18	-36.6	(37.18)
<b>Transferrin Saturation (%)</b>						
Baseline	18	35.6	(14.72)	18	37.3	(11.39)
Change from Baseline to Day 8	18	-0.2	(27.82)	18	5.4	(31.47)
Change from Baseline to Day 15	18	12.6	(41.69)	17	18.1	(34.06)
Change from Baseline to Day 22	18	6.2	(26.30)	17	8.6	(28.04)
Change from Baseline to Day 29	17	-17.0	(15.56)	18	-1.4	(19.86)
Change from Baseline to Last Visit	18	-15.7	(16.12)	18	-1.4	(19.86)

**FIG. 59**

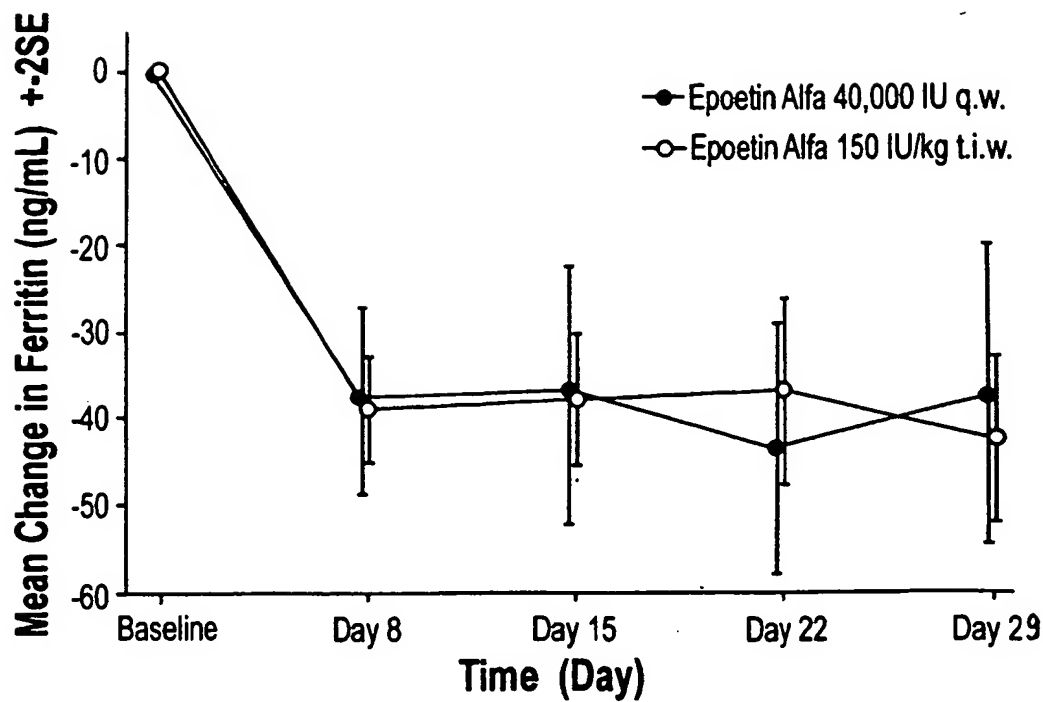


FIG. 60

# **SUBJECTS WITH HIGH BLOOD PRESSURE VALUES <sup>a</sup>**

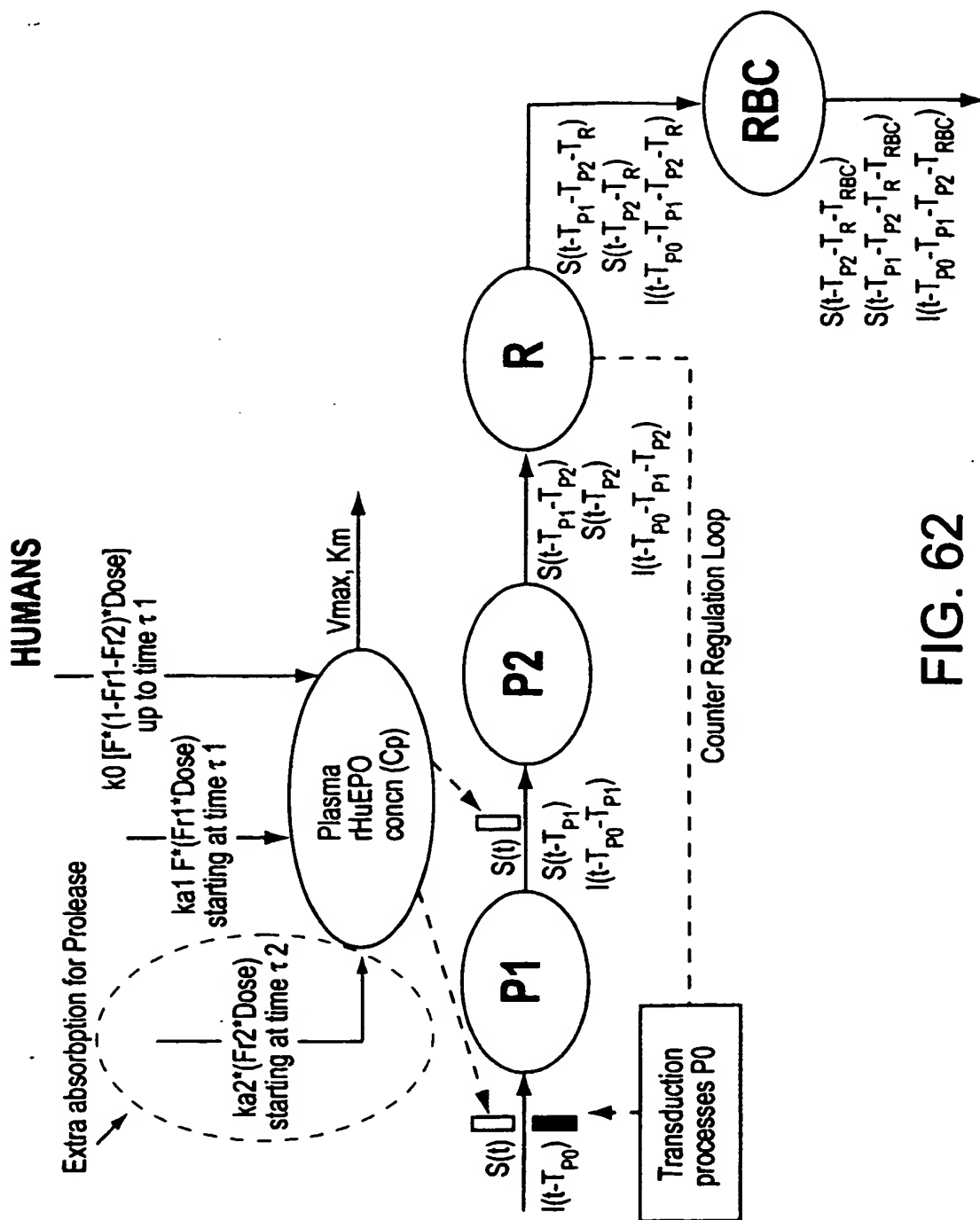
SUBJECT	PRESTUDY	DAY 1	DAY 8	DAY 15	DAY 22	DAY 29
<b>Epoetin Alfa 150 IU/kg t.i.w.</b>						
1005	119/69	129/72	119/62	140/87 <sup>b</sup>	127/70	121/72
2015	134/62	146/77 <sup>b</sup>	144/64 <sup>b</sup>	139/75	127/69	142/88 <sup>b</sup>

<sup>a</sup> As indicated by a systolic blood pressure  $\geq$  140 mmHg or a diastolic pressure  $\geq$  95 mmHg.

<sup>b</sup> Indicates a systolic blood pressure  $\geq$  140 mmHg.

**FIG. 61**





**FIG. 62**

## PHARMACOKINETIC PARAMETERS AFTER rHuEpo DOSING

	EPREX <i>single dose</i>	PROLEASE
ka1 (hr <sup>-1</sup> )	0.0219	0.0084
ka2 (hr <sup>-1</sup> )	-	0.0027
fr1	0.1308	0.3643
fr2	-	0.0782
kel (hr <sup>-1</sup> )	-	0.0027
Vmax (IU/kg/hr)	138.5	-
Km (IU/L)	20940	-
Vd (L/kg)	0.0558	0.2072
Tau1 (hr)	44	45.18
Tau2 (hr)	-	215.2
F=0.3884+0.00024952*DOSE		

For EPREX 150 IU/kg/t.i.w	600 IU/kg/wk
0.1193	-
10	32.15
F=0.25	

FIG. 63

**PHARMACODYNAMIC PARAMETERS AFTER rHuEpo DOSING  
PHYSIOLOGICAL/LIFESPAN PARAMETERS ESTIMATED FROM  
SINGLE DOSE DATA**

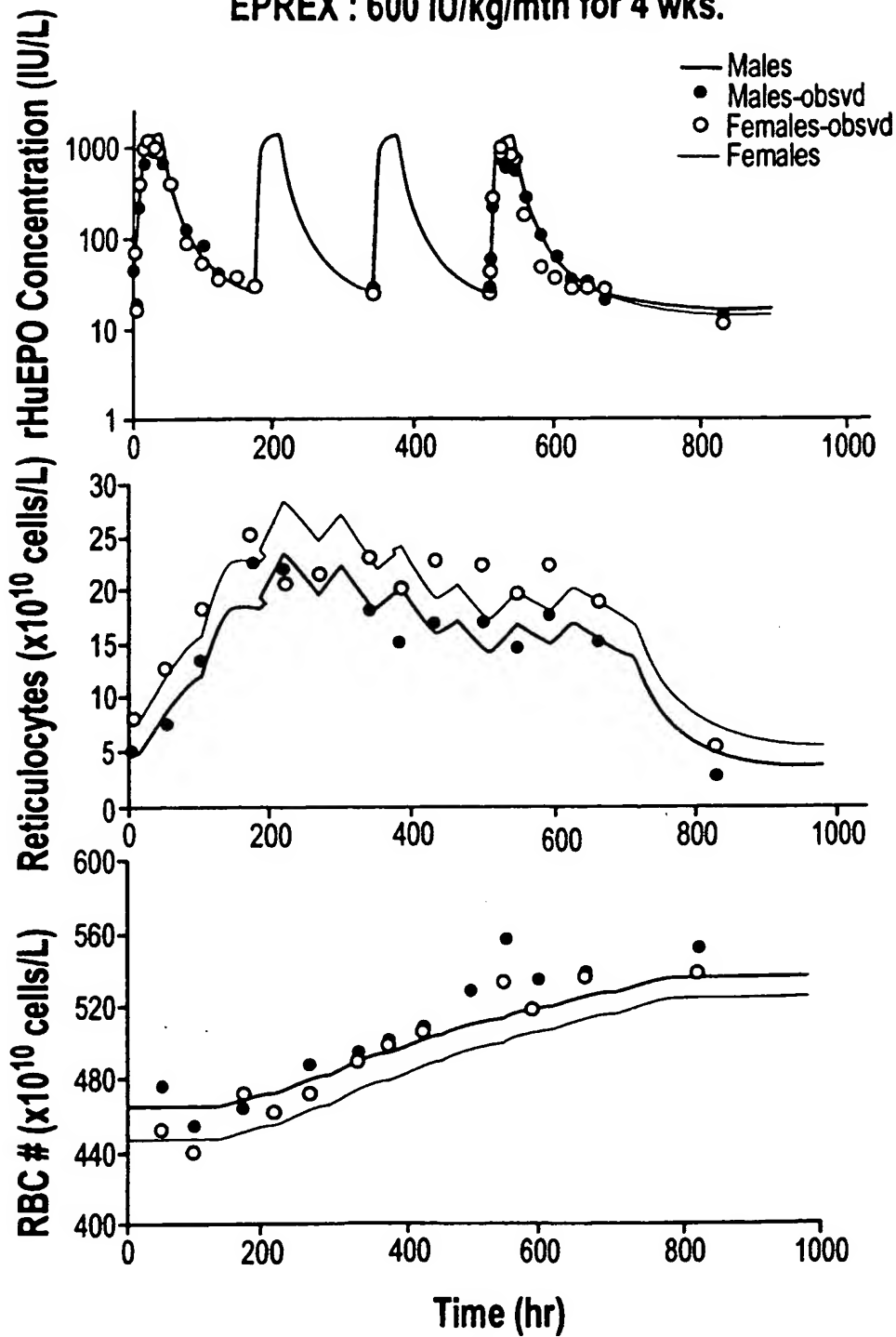
TP1	88.17
TP2	10.76
*RL	116.6
**IC50	38.71
TPO	137.5

**EPREX**

single dose	multiple dosing	
* (males)	males	females
** 4.251	8.186	4.178
26.53	61.15	57.3

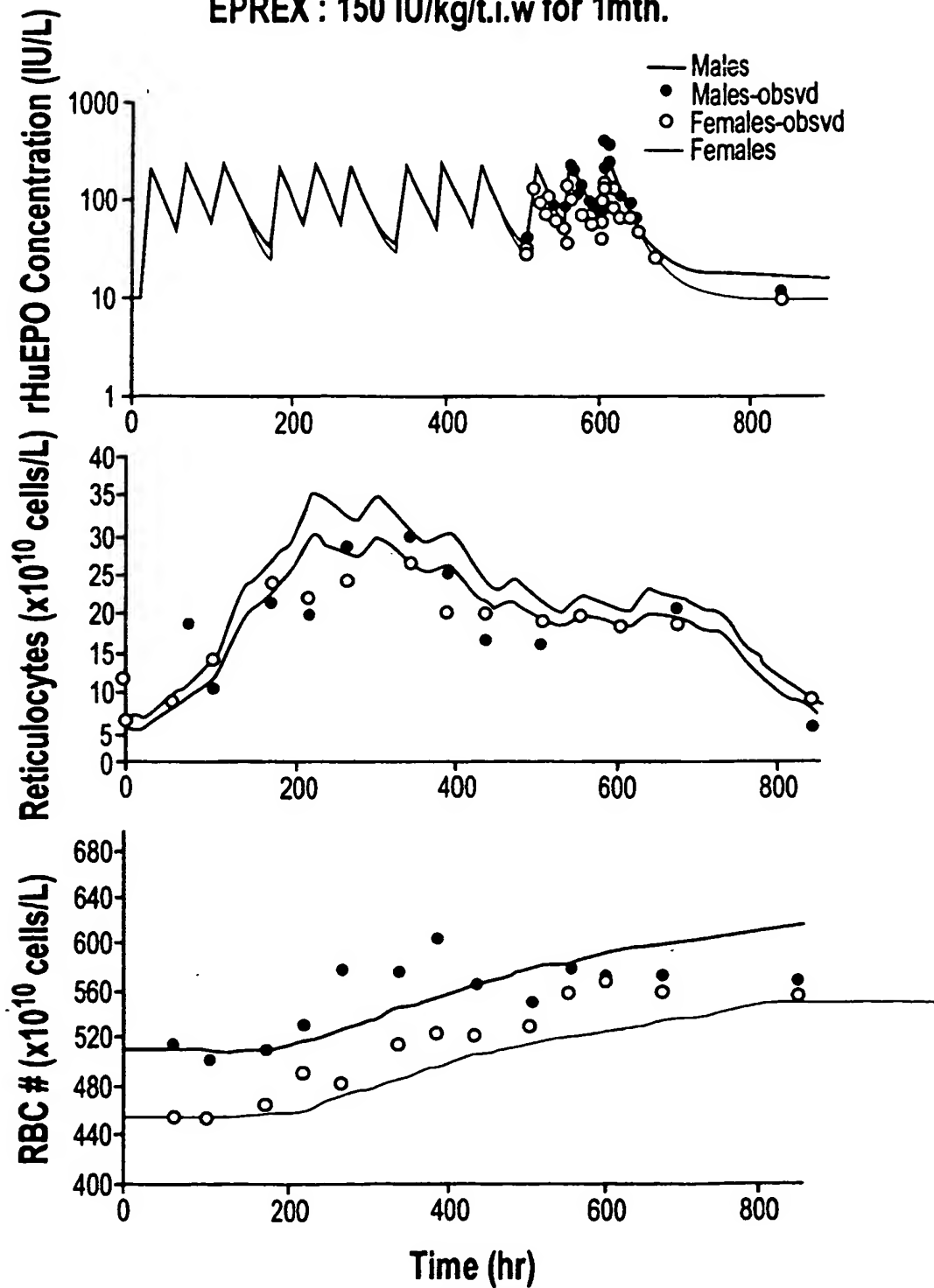
**FIG. 64**

**INT-57 Surgery arm**  
**EPREX : 600 IU/kg/mth for 4 wks.**

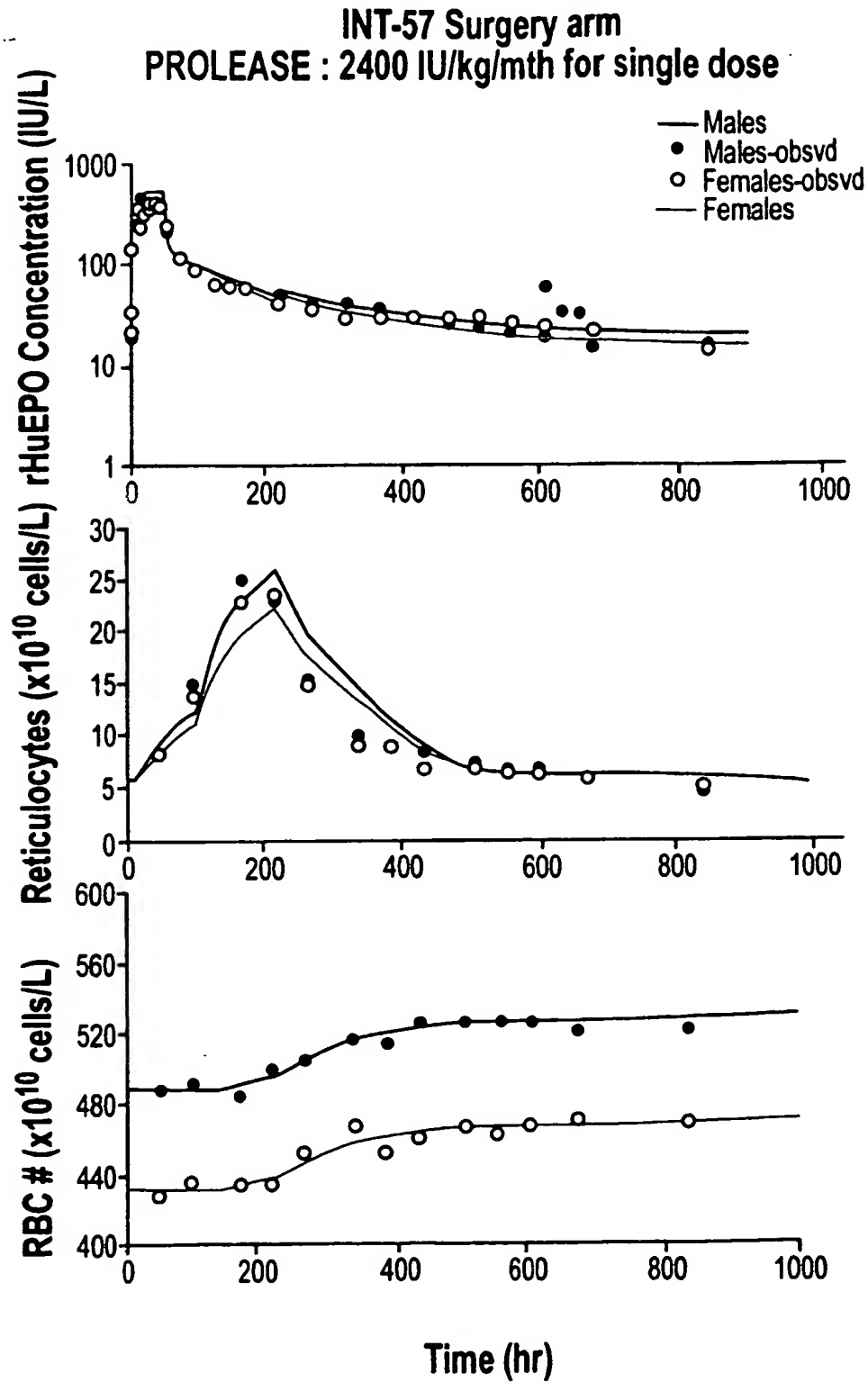


Time (hr)  
**FIG. 65**

**INT-57 Surgery arm**  
**EPREX : 150 IU/kg/t.i.w for 1mth.**

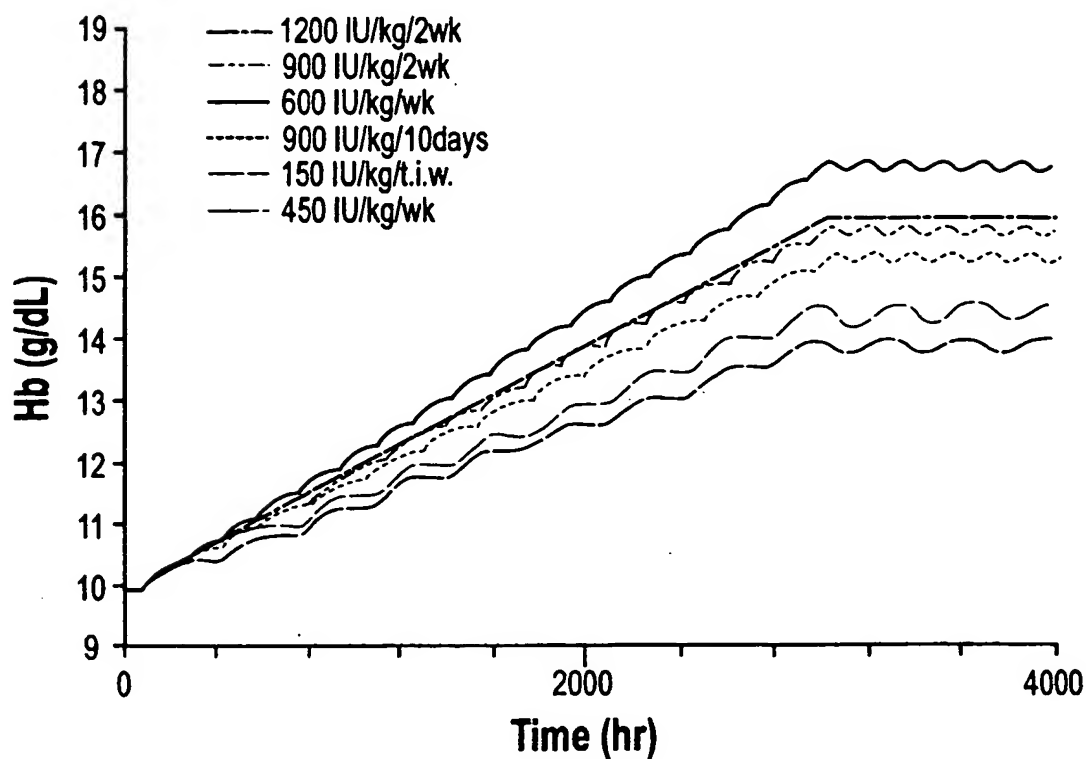


**FIG. 66**



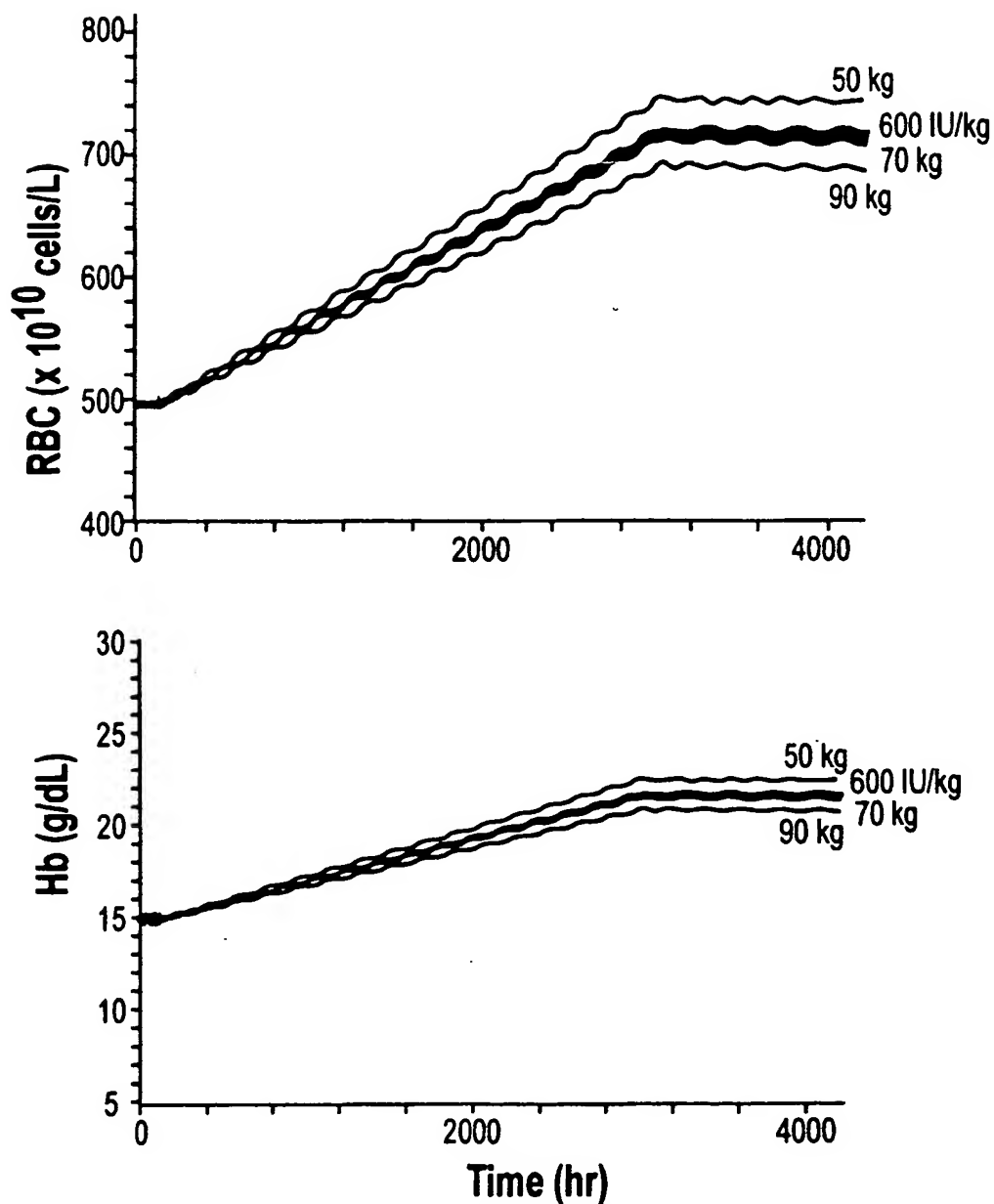
**FIG. 67**

**Simulations of Hb levels after  
administration of different doses/regimens  
of rHuEpo  
(baseline of 40U/l; threshold of 22.58 U/l)**



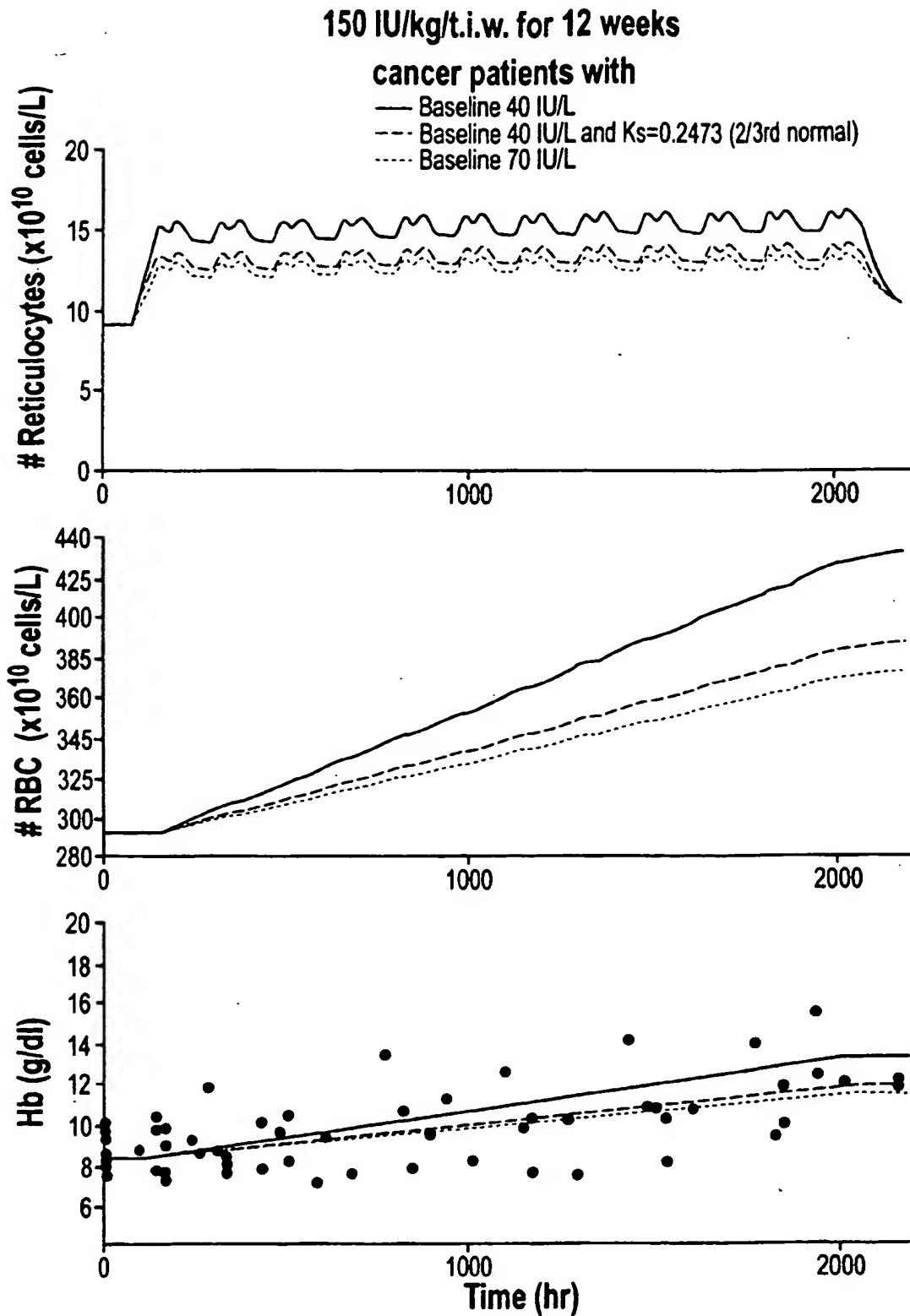
**FIG.68**

**40000 IU/wk for 50, 70 and 90kg subjects  
versus 600 IU/kg/wk**

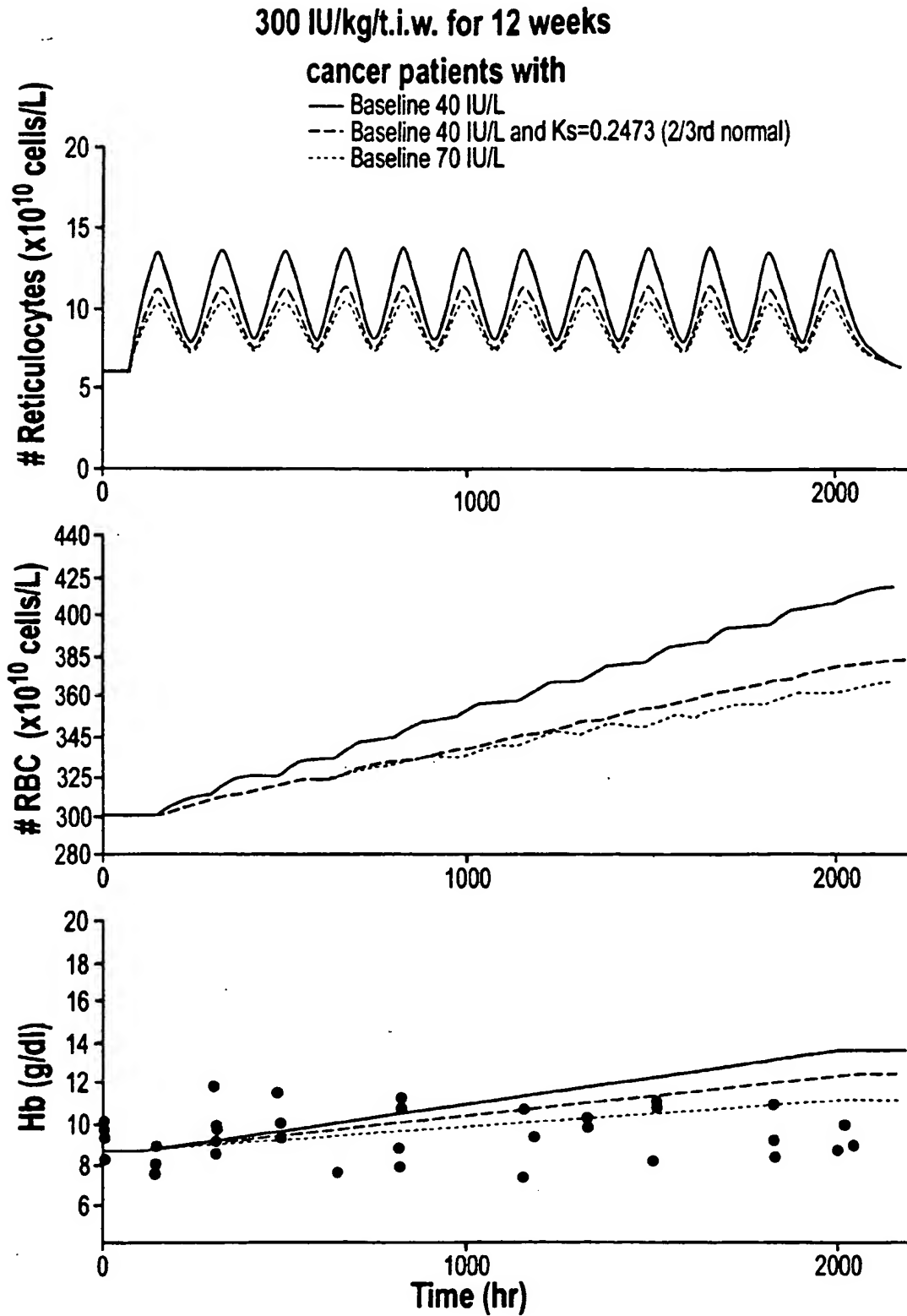


**FIG.69**





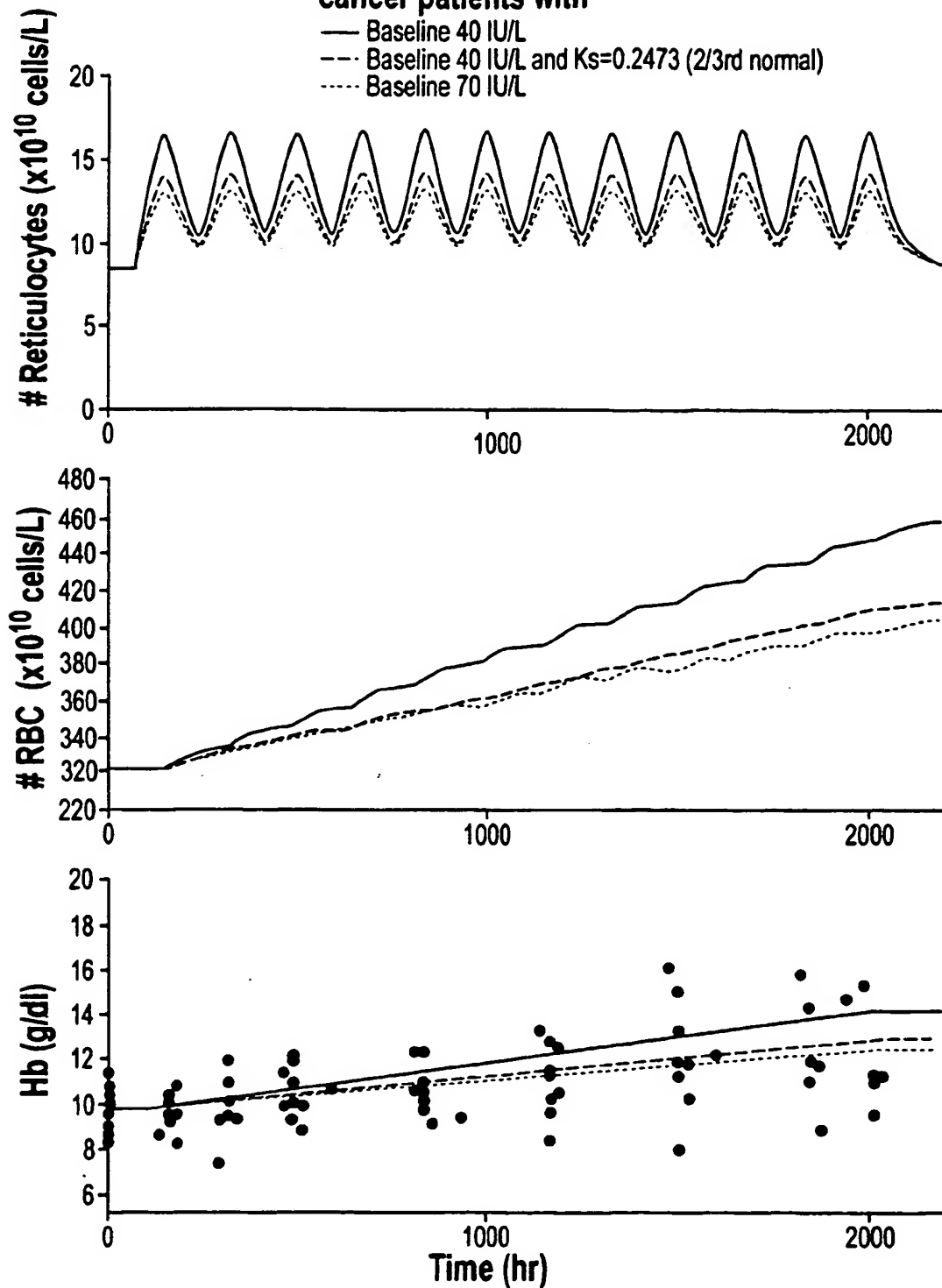
**FIG. 70A**



**FIG. 70B**

**450 IU/kg/wk for 12 weeks**

**cancer patients with**



**FIG. 70C**

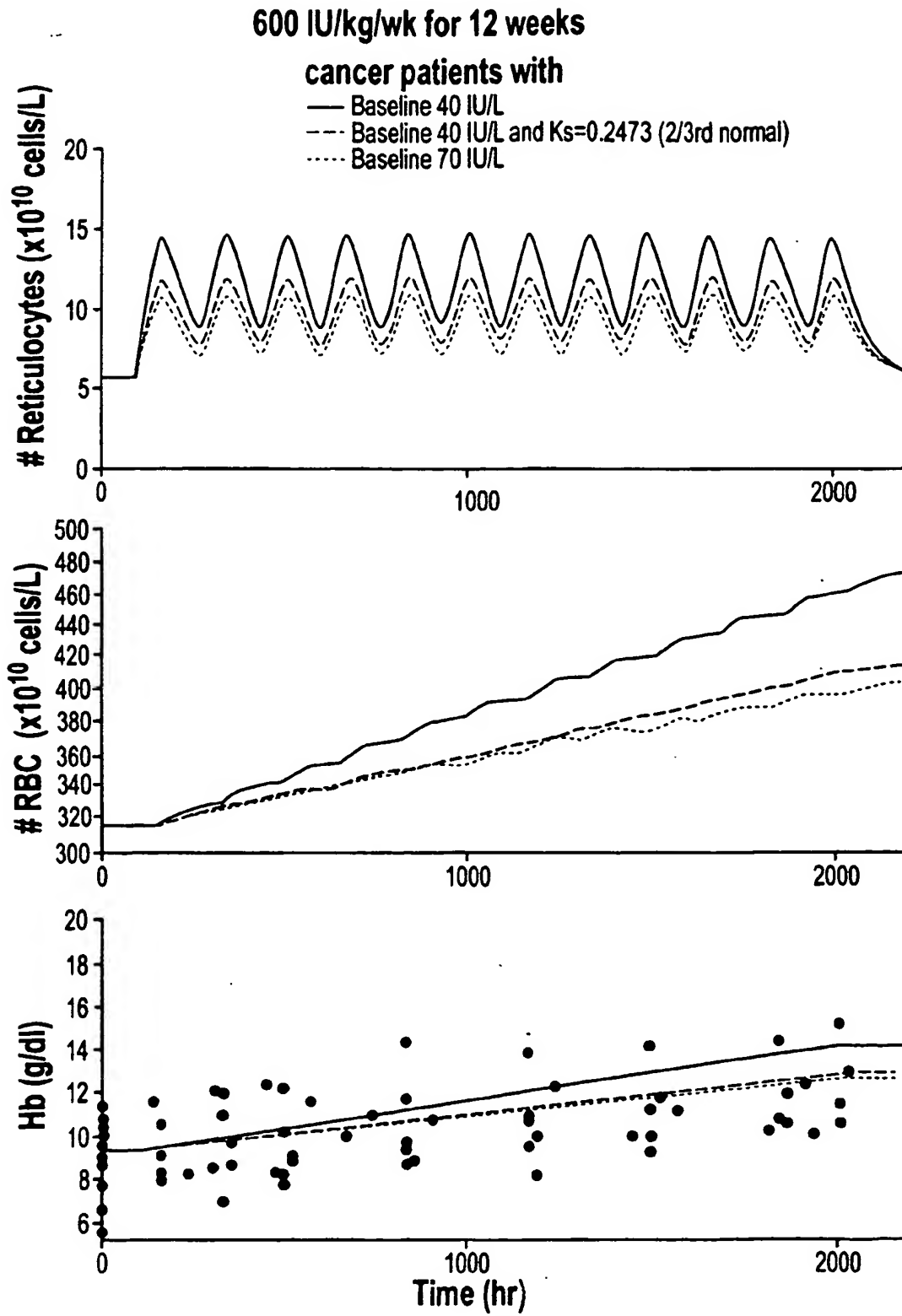
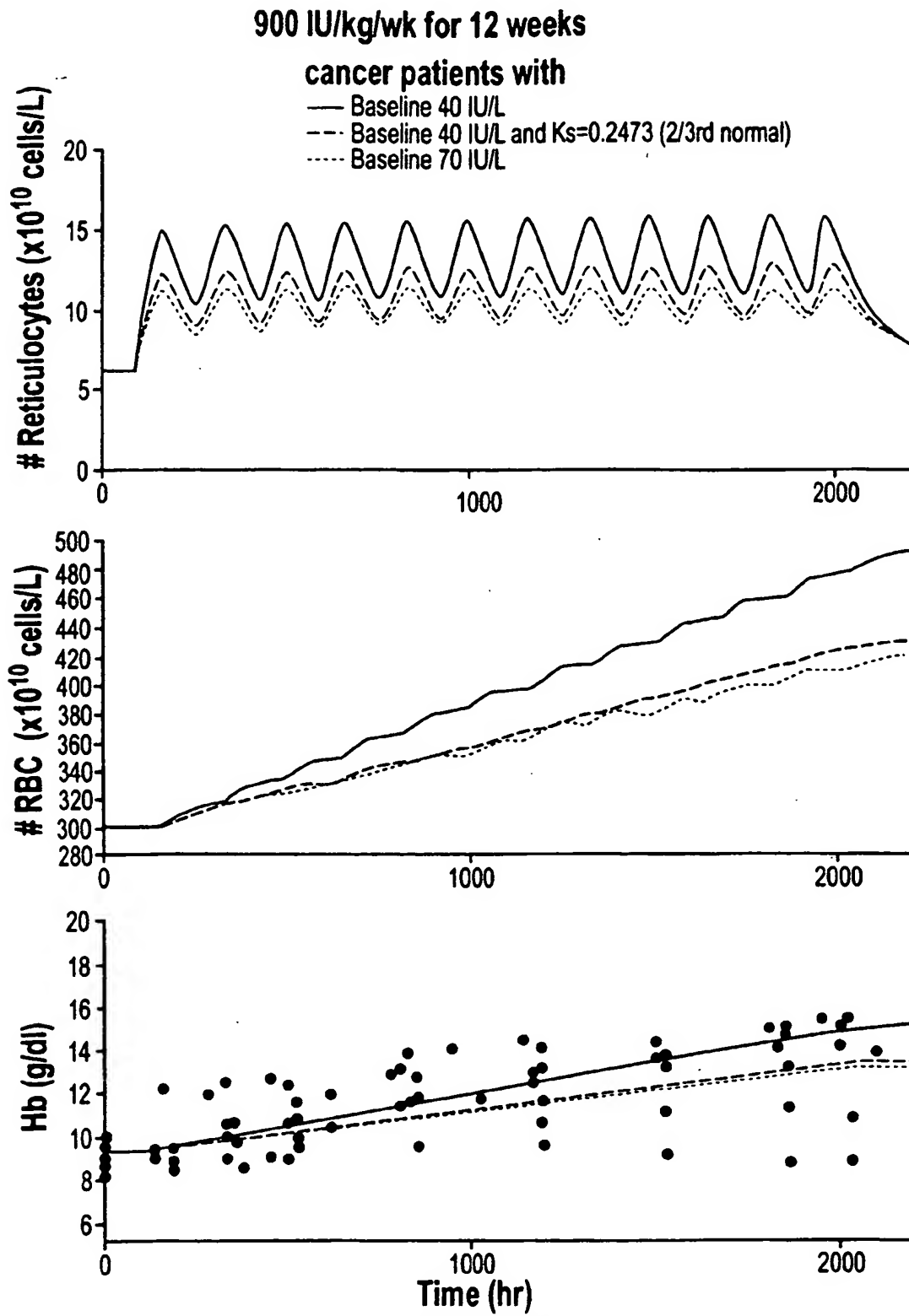
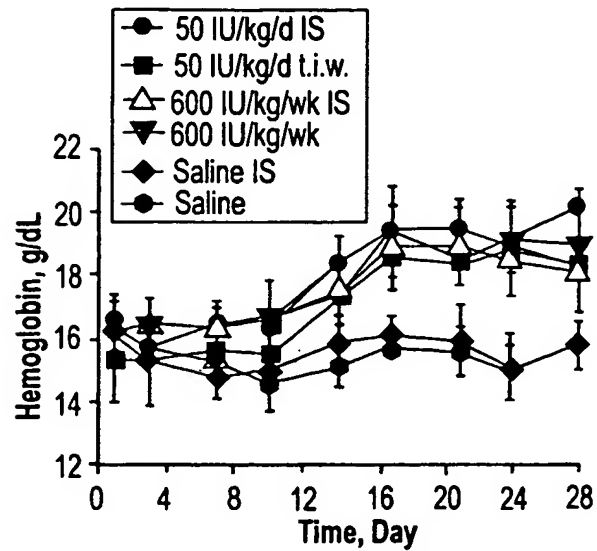


FIG. 70D

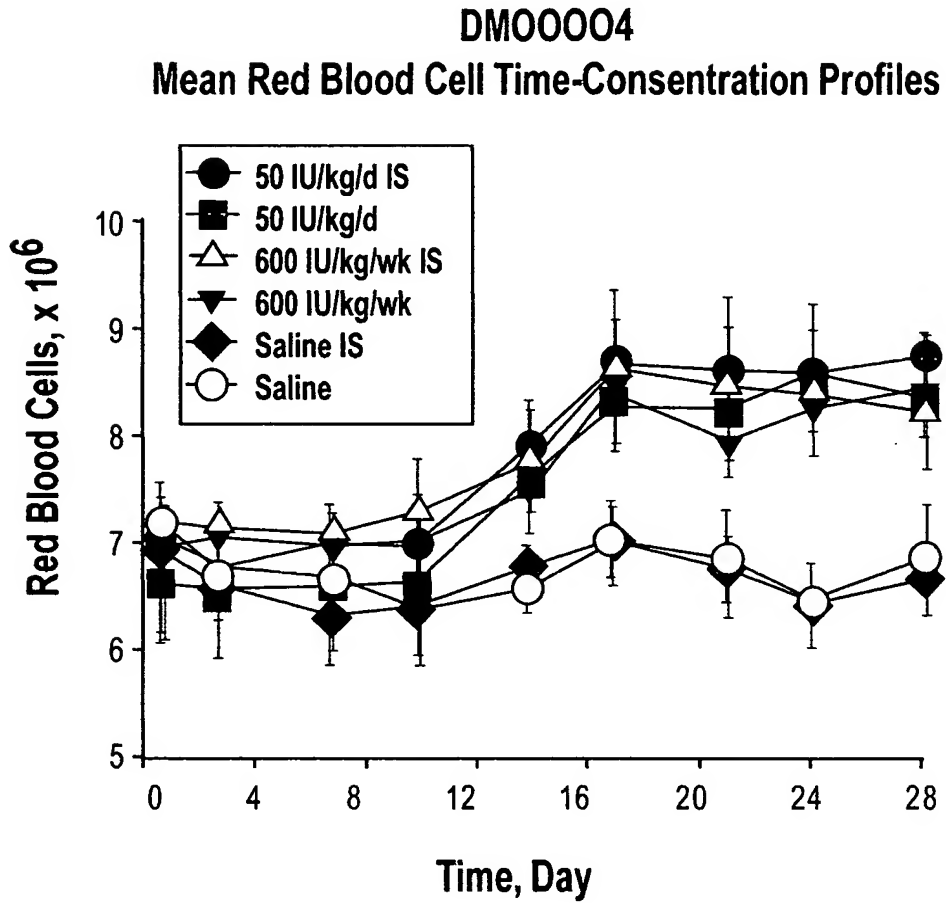


**FIG. 70E**

**DM00004**  
**Mean Hemoglobin Time-Concentration Profiles**



**FIG. 71**



**FIG.72**

# PK/PD MODEL FOR rHuEpo IN MONKEYS

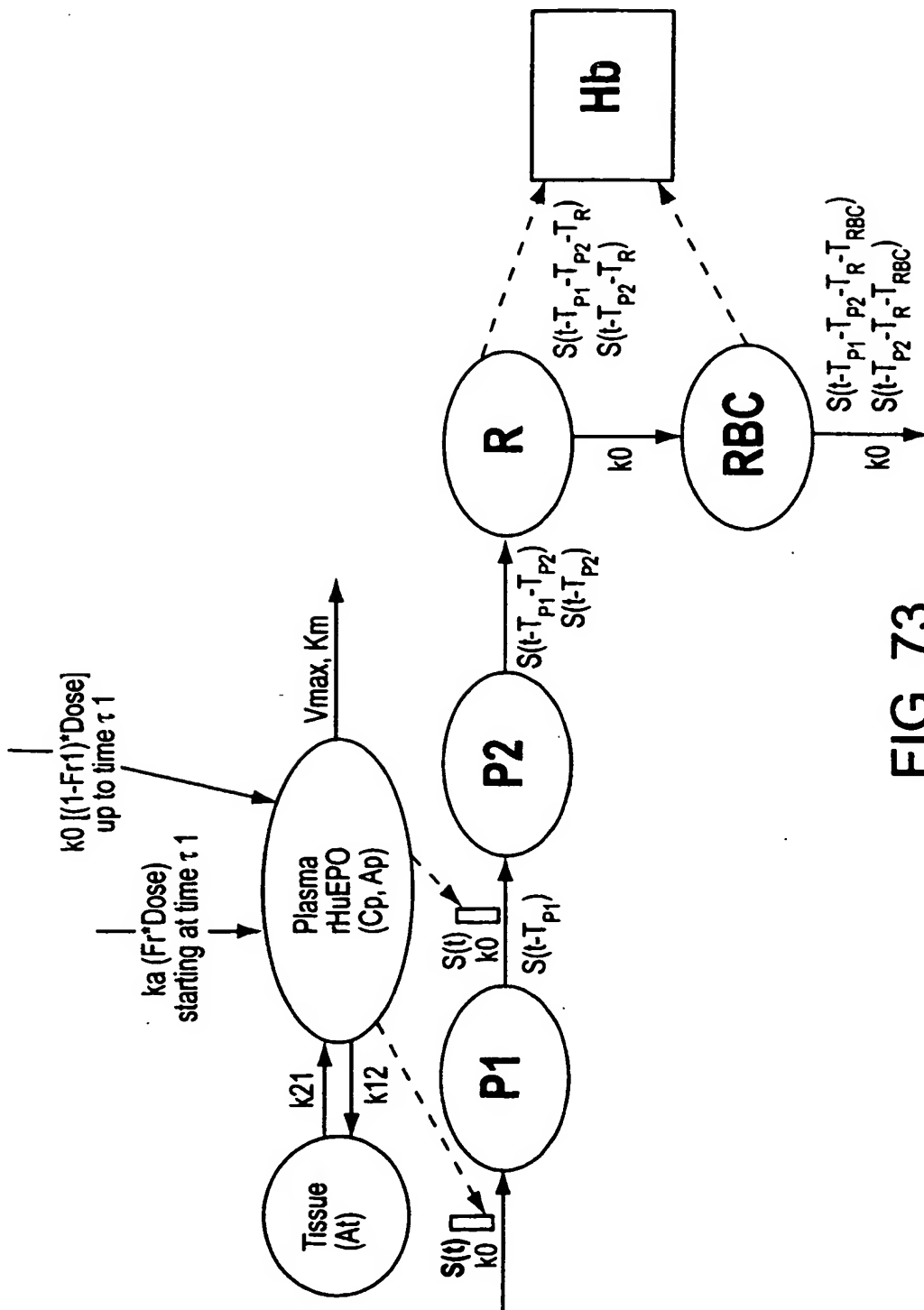


FIG. 73



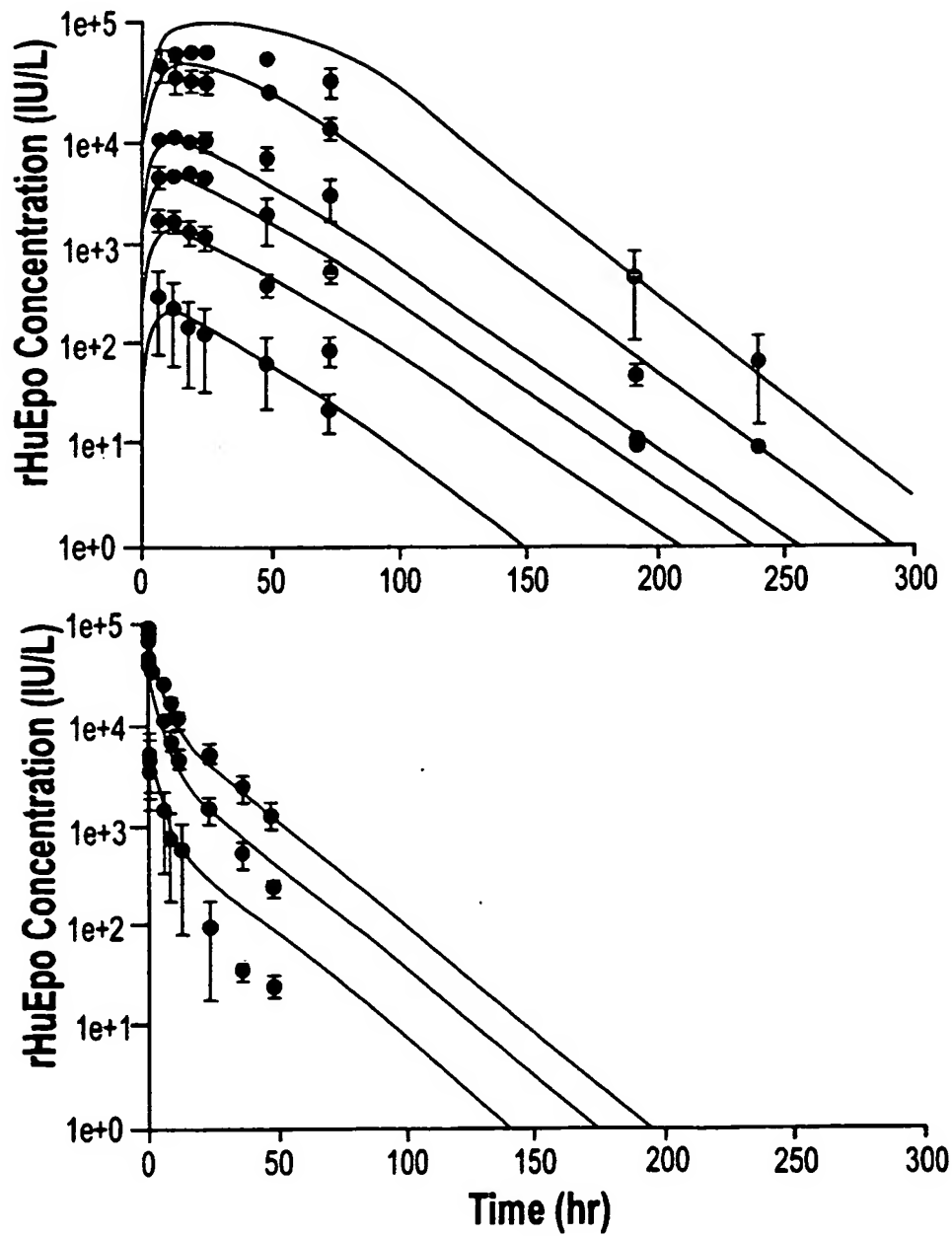


FIG. 74

## PHARMACOKINETIC PARAMETERS IN MONKEYS

	EPREX
Vmax (IU/kg/hr)	480.3
Km (IU/L)	35190
Vd (L/kg)	0.05689
k12 (hr <sup>-1</sup> )	0.1192
k21 (hr <sup>-1</sup> )	0.07916
Tau (hr)	10
ka (hr <sup>-1</sup> )	0.04427
ka (hr <sup>-1</sup> )-lowest dose	0.05255
Fr	0.6452
F (400 IU/kg dose)	0.2666
F (1000 IU/kg dose)	0.7348
F (higher doses)	1

FIG. 75

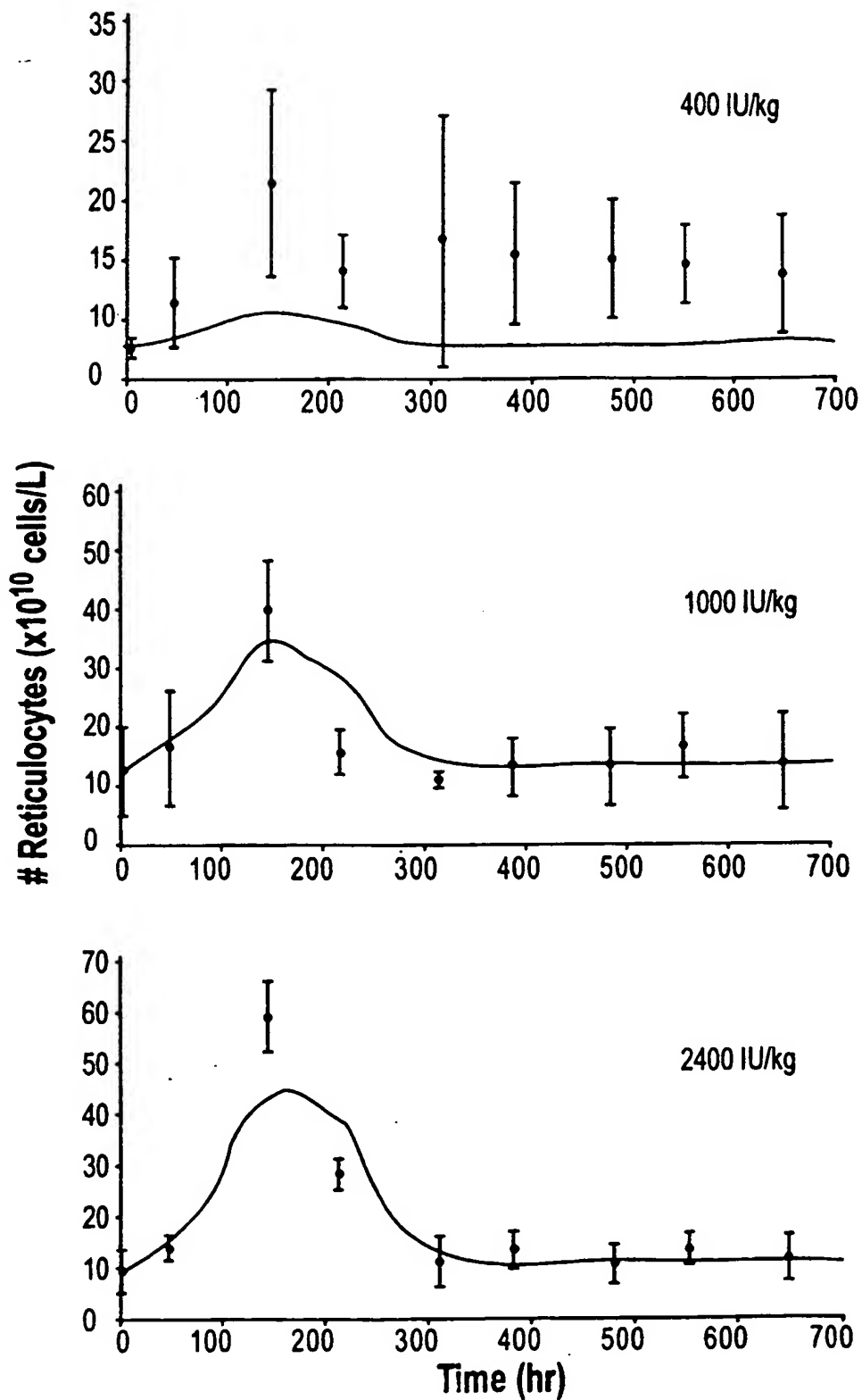


FIG. 76A

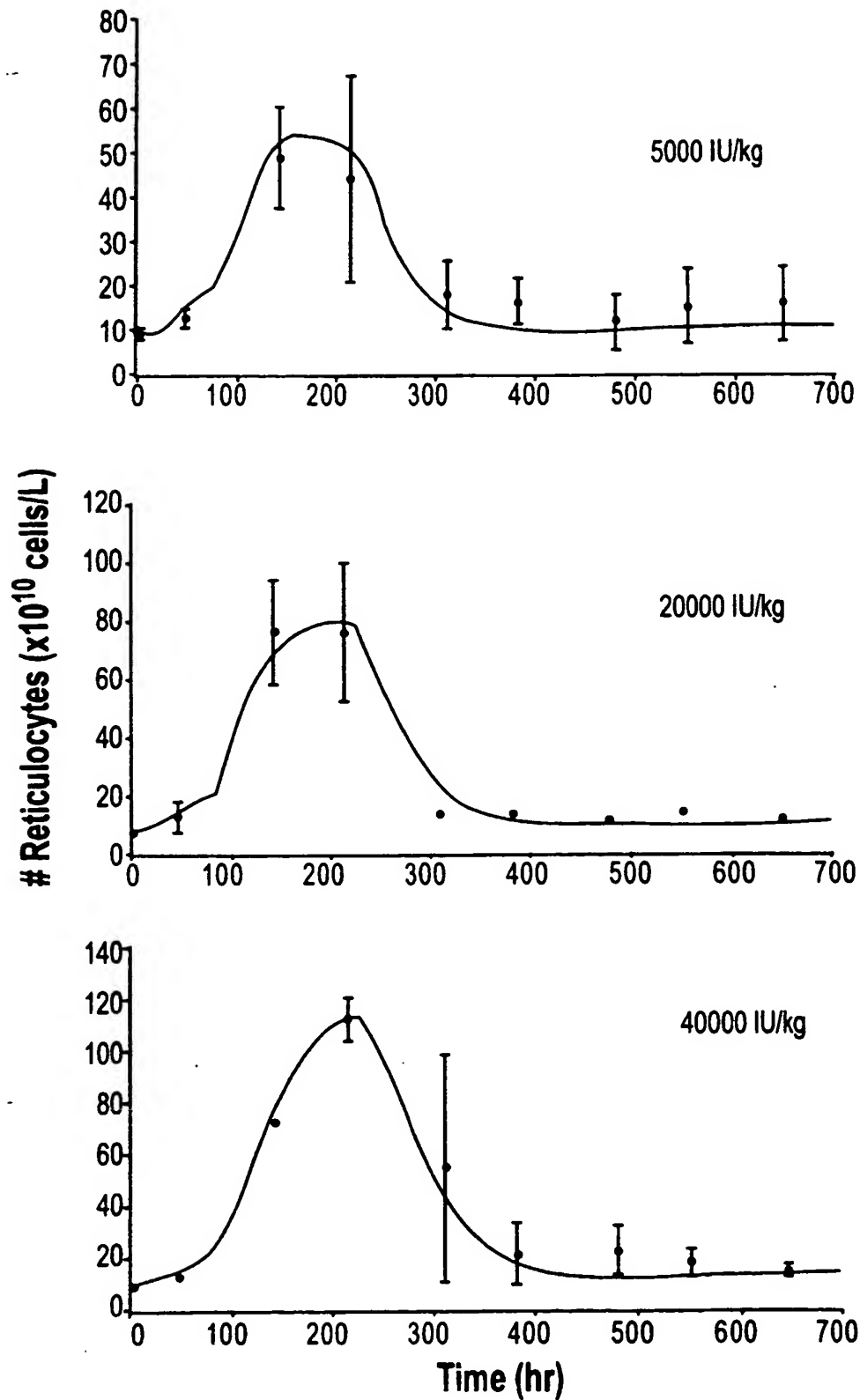


FIG. 76B

## PHARMACODYNAMIC PARAMETERS IN MONKEYS

	EPREX
TP1 (h)	70.38
TP2 (h)	14.95
RL (h)	141.6
Smax	3.133
SC50 (IU/L)	842.5

FIG. 77

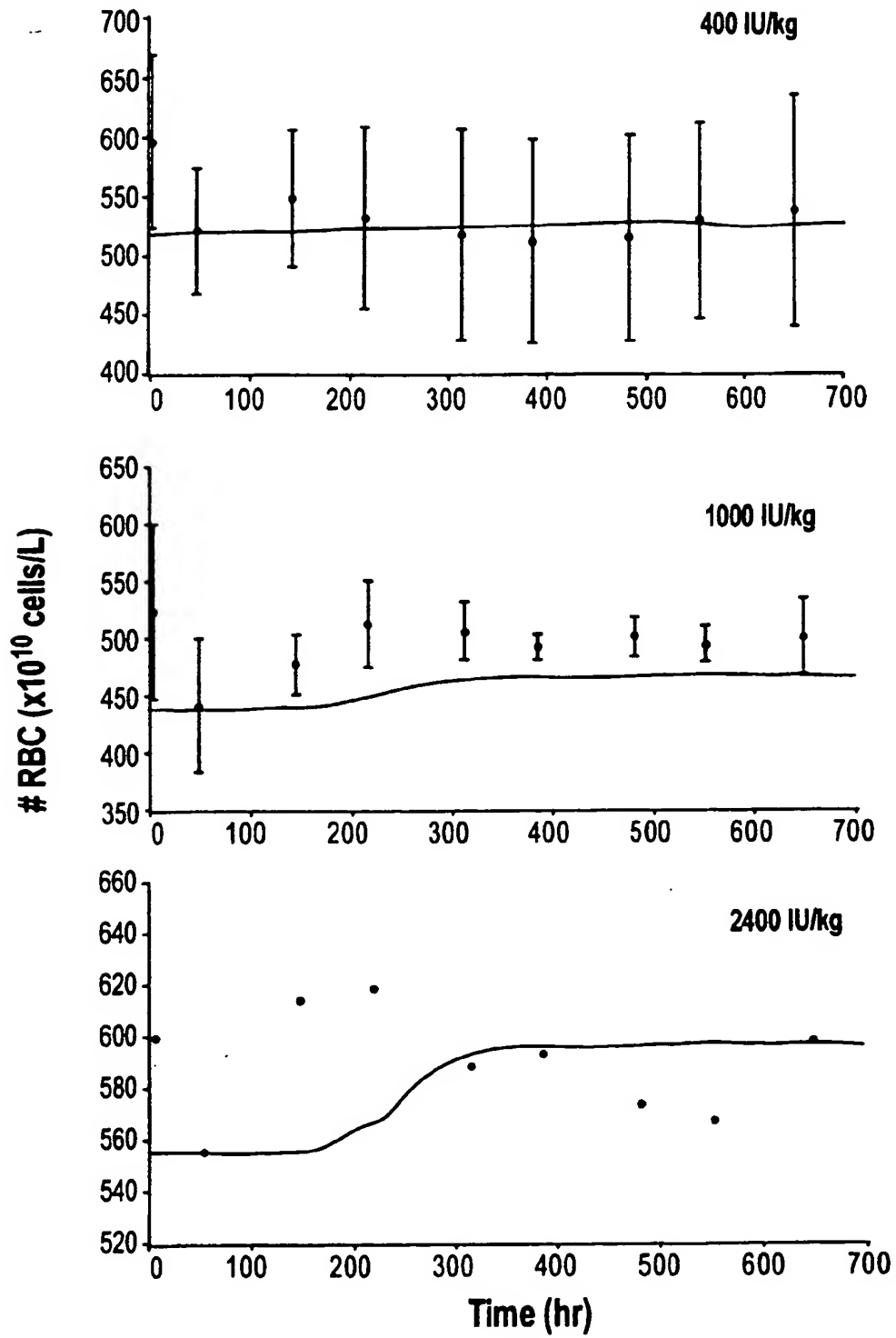


FIG. 78A

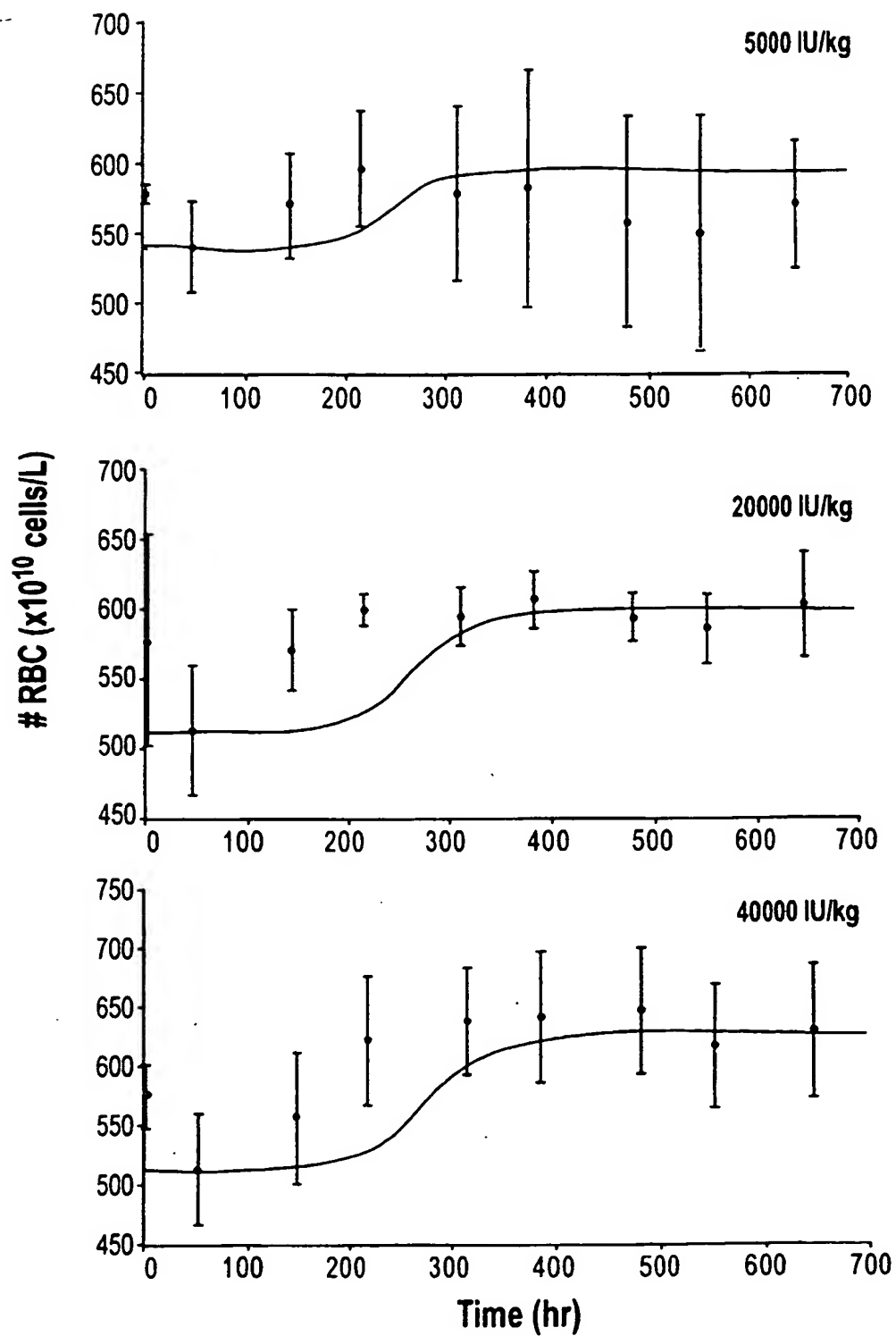


FIG. 78B

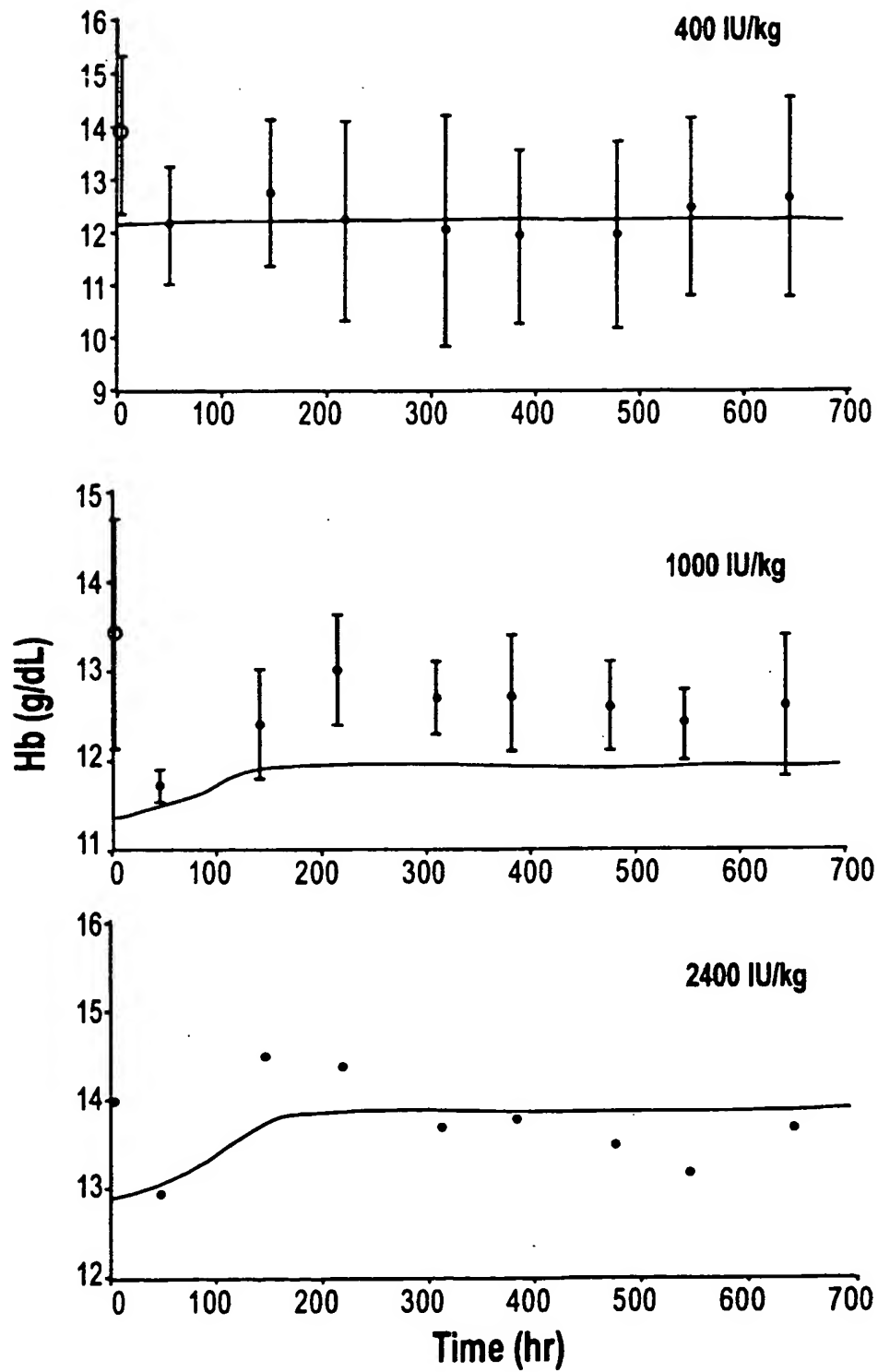


FIG. 79A



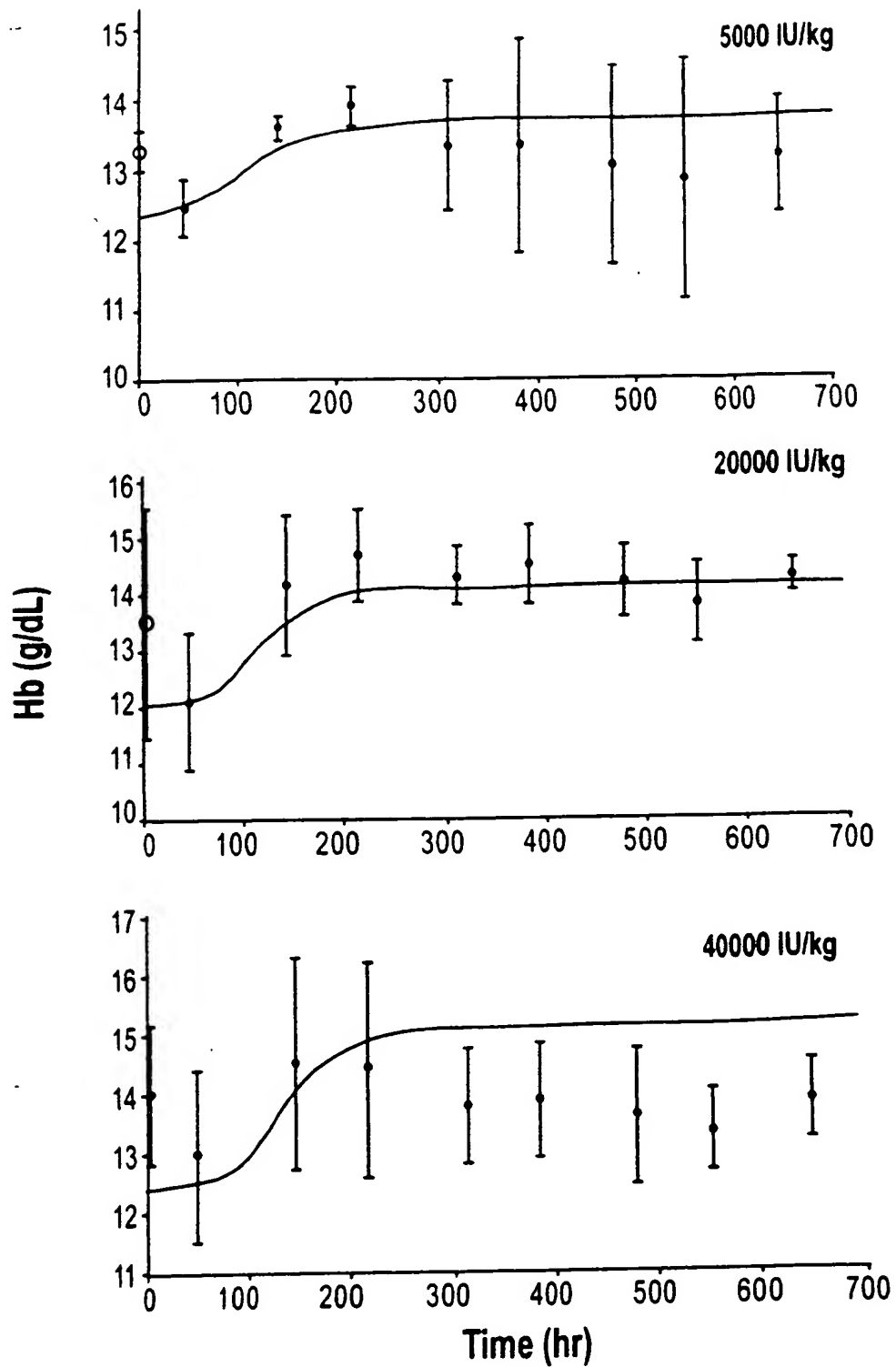


FIG. 79B

## PHARMACODYNAMIC PARAMETERS IN HUMANS

	EPREX
TP1 (h)	88.17
TP2 (h)	10.76
RL (h)	116.6
Smax	4.251
SC50 (IU/L)	26.53
TP0 (h)	137.5
IC <sub>50</sub> (x10 <sup>10</sup> Reti/L)	38.71

FIG. 80

# PK/PD MODEL FOR rHuEpo IN HUMANS

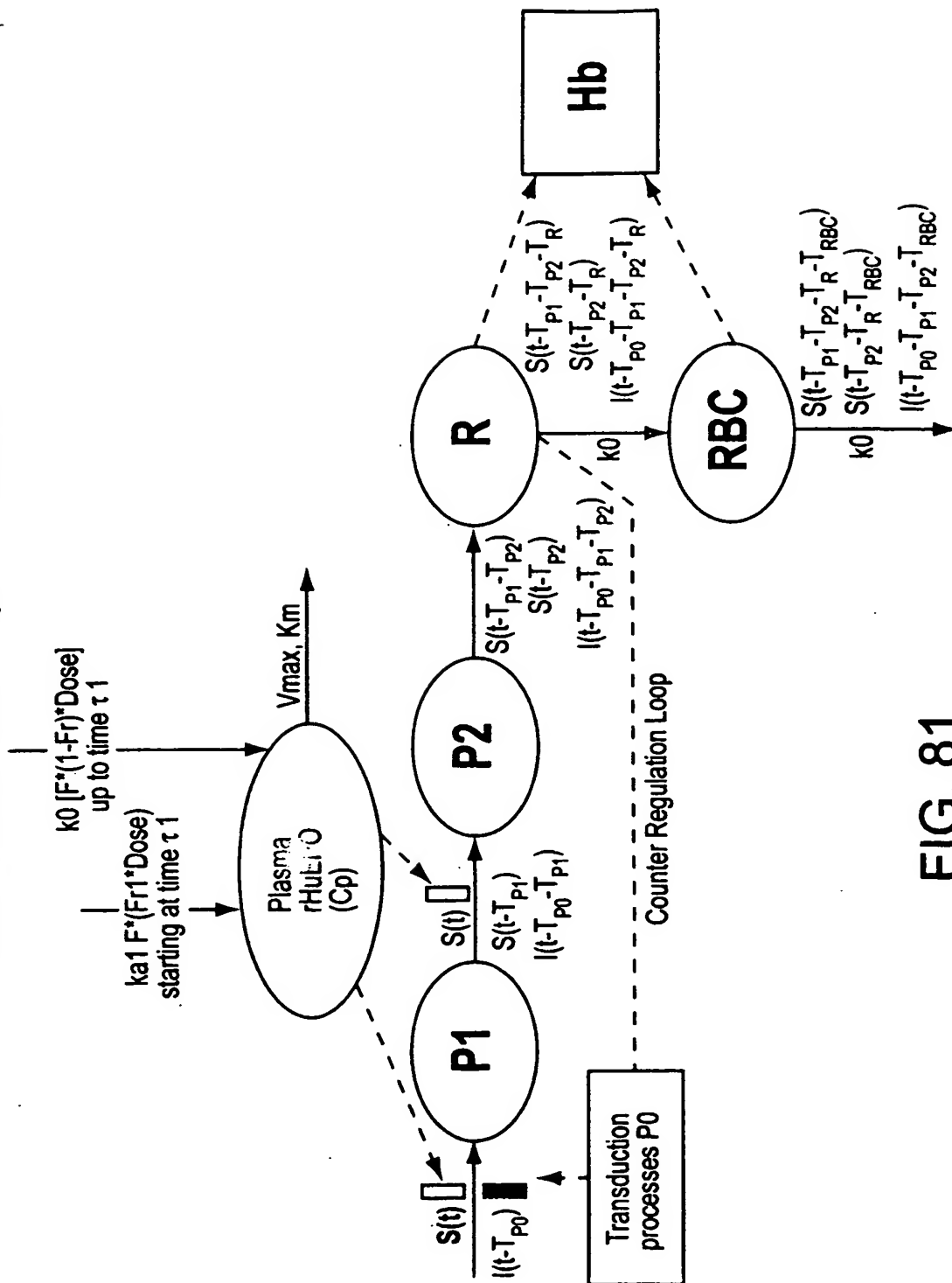


FIG. 81